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Señor
SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E. S. D.

Re: P1.-**F. HOFFMANN-LA ROCHE AG**-Solicitud de Patente de Invención en Fase Nacional PCT para "**ÁCIDO BISFOSFÓNICO PARA EL TRATAMIENTO Y PREVENCIÓN DE OSTEOPOROSIS**".-Clase **A61P 19/10**.-Expediente número **04-096.462.-**

1. Me refiero al auto dictado por ese Despacho notificado por fijación en lista el 14 de Marzo de 2008.

2. Con el fin de responder a las objeciones expuestas por el señor Examinador en su Concepto Técnico No. **422** bajo los acápites de Claridad de la solicitud y Reivindicaciones relativas a un uso o a un segundo uso, atentamente me permito presentar los siguientes argumentos técnicos y las siguientes modificaciones hechas en el capítulo reivindicatorio de la presente solicitud, mediante lo cual no sólo se superan dichas objeciones, sino que además se demuestra en forma contundente la patentabilidad de la presente solicitud.

3. **MODIFICACIONES A LA SOLICITUD**

Incialmente me permito manifestar que el solicitante de la invención en cuestión ha decidido presentar un nuevo capítulo reivindicatorio, el cual está compuesto por seis (6) reivindicaciones cuyo sustento se analiza a continuación:

- La nueva reivindicación 1 está dirigida a proteger un medicamento que comprende 100 mg ó 150 mg de un ácido bisfosfónico (o una sal

farmacéuticamente aceptable del mismo) junto con uno o más excipientes farmacéuticamente aceptables. Dicha nueva reivindicación presenta adecuado sustento en la páginas 6 (líneas 14 a 17) y 14 (líneas 1 a 6) de la memoria descriptiva originalmente presentada.

- La nueva reivindicación 2 define que el ácido bisfosfónico mencionado en la nueva reivindicación 1 es específicamente el ácido ibandrónico. Lo anterior presenta pleno sustento, por ejemplo, en la página 11 (líneas 17 a 20) de la descripción de la presente solicitud de patente.

- Las nuevas reivindicaciones 3 y 4 se encuentran dirigidas a proteger un medicamento de acuerdo con las reivindicaciones precedentes, el cual se caracteriza porque contiene específicamente 100 mg y 150 mg de ácido bisfosfónico (o una sal farmacéuticamente aceptable del mismo), respectivamente. En este caso, es claro que el sustento para dichas nuevas reivindicaciones es la nueva reivindicación 1, y por ende, la materia descrita en la página 6 (líneas 14 a 17) de la descripción.

- La nueva reivindicación 5 especifica que el ácido bisfosfónico (o la sal farmacéuticamente aceptable del mismo) mencionado en las reivindicaciones 1 a 4 precedentes es la sal monosódica del ácido ibandrónico monohidrato, de acuerdo a lo establecido en la página 13 (líneas 3 a 6) de la memoria descriptiva de la presente solicitud de patente).

- La nueva reivindicacion 6 está dirigida a proteger un medicamento de conformidad con lo descrito en las reivindicaciones 1 a 5 precedentes, el cual adicionalmente está caracterizado porque es un comprimido recubierto por una película, cuyo núcleo está conformado por 100 mg ó 150 mg de un ácido bisfosfónico (o una sal farmacéuticamente aceptable de este) y uno o más excipientes escogidos entre: lactosa, polivinilpirrolidona, celulosa microcristalina, crospovidona, ácido esteárico, dióxido de silicio, hidroxipropil metilcelulosa, óxido de titanio, talco y polietilenglicol 6000. Dicha nueva reivindicación presenta adecuado sustento en la página 14 (líneas 2 a 24) de la descripción originalmente presentada.

En vista de lo anterior, atentamente me permito resaltar que las modificaciones realizadas al capítulo reivindicatorio de la presente solicitud de patente **no amplían de manera alguna el alcance establecido en la memoria descriptiva originalmente presentada.** En este sentido, es claro que dichas modificaciones han sido realizadas con el único fin de cumplir con los requisitos de patentabilidad estipulados en la Decisión 486.

4. **CLARIDAD DE LA SOLICITUD**

El señor Examinador ha objetado la claridad de la presente solicitud con base en los siguientes argumentos:

DESCRIPCIÓN

> ***"No se encontraron datos comparativos con las composiciones previamente divulgadas que demuestren su aporte al estado de la técnica, y el efecto inesperado alcanzado"***

En respuesta a lo anterior, atentamente me permito poner en consideración del señor Examinador los siguientes documentos que permiten demostrar el sorprendente aporte al estado de la técnica brindado por la materia revelada en la presente solicitud de patente:

- **Epstein Solomon;** "Ibandronate Treatment for Osteoporosis: Rationale, Preclinical, and Clinical Development of Extended Dosing Regimens"; *Current Osteoporosis Reports; 2006; 4 (1); 14-20;* ***(Anexo A)***

- ***Once monthly dosing increases the proportion of patients who respond to oral ibandronate: 1-year results from MOBILE;*** *J. Bone Miner. Res.; Res 2004; 19 (Suppl. 1):S447 (Abstract M432);* ***(Anexo B)***

- **Monthly oral ibandronate significantly reduces bone resorption in postmenopausal osteoporosis: 1-year results from MOBILE;** J. Bone Miner. Res.; 2004; 19 (Suppl.1):S94 (Abstract F406); **(Anexo C)**

Con respecto al anexo A, considero de especial importancia resaltar los comentarios realizados por el autor de dicho documento en el tercer párrafo de las conclusiones (página 19); allí se establece que antes de los estudios experimentales que condujeron a obtener la sorprendente información revelada en la presente solicitud de patente, se asumía como parte del estado de la técnica que debido a que los osteoclastos tienen una vida media de entre 2 y 3 semanas, dicho rango era el máximo intervalo de tiempo que debía existir entre la administración de bisfosfonatos a un paciente en tratamiento. Sin embargo, en dicho documento se concluye que los estudios con ibandronato han demostrado que el intervalo de dosis puede ser extendido a un (1) mes sin que se vea alterada la eficacia del tratamiento.

Por su parte, con base en los estudios clínicos revelados en el anexo B, los autores de dicho documento concluyen que la gran mayoría de mujeres a las que se les administró mensualmente 100 mg o 150 mg de ibandronato lograron incrementos significativos en la densidad mineral ósea tanto en la espina lumbar (LS BMD), como en la cadera (HT BMD). Así, por ejemplo, de acuerdo a los datos revelados en la tabla 1 de dicho anexo B, es claro que un 91.3% de pacientes a las que se les administró mensualmente 150 mg de ibandronato mostraron un aumento en la densidad mineral ósea de la espina lumbar (LS BMD), mientras que sólo un 84% de pacientes a quienes se les administró diariamente 2.5 mg de ibandronato mostraron un aumento en LS BMD. Asimismo, un mayor porcentaje de pacientes a las que se les administró mensualmente 100 mg (87.1%) y 150 mg (90.0%) de ibandronato lograron aumentos substanciales en la densidad mineral ósea en la cadera (TH BMD), pues sólo un 76.7% de pacientes a las que se les administró diariamente 2.5 mg de ibandronato lograron incrementos similares en TH BMD.

Finalmente, en el anexo C básicamente se revela que la administración mensual de 150 mg de ibandronato a pacientes con osteoporosis postmenopáusica suprime marcadamente la magnitud de CTX en suero (enlaces de colágeno carboxi-terminal). Como consecuencia de lo anterior, la administración mensual de 150 mg de ibandronato suprime rápidamente la resorción ósea hasta niveles normales luego de tres meses de haber iniciado el tratamiento, con la característica adicional de que dicha supresión se mantiene mientras se mantenga el mismo esquema de administración del medicamento.

En síntesis, atentamente me permito resaltar ante ese Despacho que **los documentos previamente mencionados muestran claramente que el medicamento revelado en el nuevo capítulo reivindicatorio de la solicitud de patente en cuestión, esto es, una dosis única mensual de 100 mg ó 150 mg de ibandronato (o una sal farmacéuticamente aceptable del mismo), presenta marcadas ventajas terapéuticas frente a las composiciones previamente conocidas en el estado de la técnica, las cuales establecen terapias de dosificación de cantidades mas bajas de ibandronato administradas en intervalos de tiempo menores.**

En este sentido, puede concluirse que: 1) la eficacia terapéutica obtenida mediante las composiciones de la presente solicitud es tan o más alta que la obtenida con las dosificaciones enseñadas en el arte previo; y, 2) la aceptación por parte de las pacientes a un régimen de tratamiento mensual con ibandronato es mucho más alta con respecto a la aceptación dada a un régimen de tratamiento diario, semanal o quincenal, como consecuencia de las implicaciones que dichas formas de dosificación tienen en los efectos laterales negativos producidos por una administración recurrente de dicho compuesto activo.

5. REIVINDICACIONES RELATIVAS A UN USO O A UN SEGUNDO USO (artículos 14 y 21 D 486)

El señor Examinador afirma lo siguiente en su Concepto Técnico:

"Las reivindicaciones 1-10, se refieren al uso de los ácidos bisfosfónicos; las cuales no son patentables de acuerdo a los artículos mencionados de la normatividad vigente"

Atendiendo a la anterior objeción y tal como se comentó en el numeral 3 del presente memorial, el solicitante de la invención en cuestión ha decidido presentar un nuevo capítulo reivindicatorio, el cual está compuesto por seis (6) reivindicaciones dirigidas exclusivamente a proteger una composición (específicamente un medicamento). En este sentido, adicionalmente resulta de gran importancia resaltar que a lo largo del nuevo capítulo reivindicatorio dicha composición se encuentra adecuadamente caracterizada por sus componentes técnicos.

En vista de lo anterior, es claro que dicho nuevo capítulo reivindicatorio cumple a cabalidad con las disposiciones establecidas en el Artículo 30 de la Decisión 486, permitiendo de esta manera superar satisfactoriamente las objeciones realizadas por el señor Examinador a éste respecto.

6. ANÁLISIS DE LA NOVEDAD Y EL NIVEL INVENTIVO

De otro lado, si bien el señor Examinador aún no ha realizado el análisis de la novedad y el nivel inventivo del nuevo capítulo reivindicatorio de la presente solicitud de patente, en su Concepto Técnico de manera absolutamente **sorprendente** hace referencia a tres documentos citados por un supuesto "opositor", cuando es absolutamente evidente que el escrito de **"remisión de información"** presentado el 6 de Octubre de 2006 por parte del Dr. Reyes Villamizar, apoderado de Tecnoquímicas S.A., fue presentado **un año y cuatro meses después de expirado el término señalado por el artículo 42 de la Decisión 486,** para que cualquier tercero con legitimo interés presente oposiciones fundamentadas. Por lo tanto, es evidente que dicho escrito no puede de ninguna forma ser tenido en cuenta por este Despacho como un escrito de oposición, pues no sólo es extemporáneo, sino que nunca fue notificado a mi representada para dar respuesta al mismo, por **no** ser efectivamente una oposición.

Sin embargo, si aún ese Despacho considera que los tres documentos citados en el escrito de Tecnoquímicas pudieran llegar a afectar la patentabilidad de la presente invención, a continuación me permito presentar una serie de argumentos claros y contundentes que desvirtuan cualquier duda que pueda llegar a surgir acerca de la patentabilidad de la invención en estudio.

6.1 Consideraciones con respecto al documento D1

En términos generales, el documento **WO 0115703** enseña métodos terapéuticos diseñados para inhibir la resorción ósea en mamíferos, donde dichos métodos se caracterizan porque permiten minimizar los efectos gastrointestinales adversos que generan los métodos terapéuticos conocidos en el estado del arte.

Específicamente, dicho documento D1 revela un método para inhibir la resorción ósea en mamíferos, que comprende la administración oral de un bisfosfonato seleccionado entre alendronato, ibandronato, risedronato y las sales o ésteres farmacéuticamente aceptables de los mismos, dentro de un horario de administración seleccionado entre: dosis una vez por semana, dosis dos veces por semana, dosis cada dos semanas y dosis dos veces al mes.

Adicionalmente, en **D1** se enseña que una unidad de dosificación para inhibir la resorción ósea en mamíferos comprende entre aproximadamente 3.5 mg y aproximadamente 200 mg de ibandronato (incluyendo las sales o ésteres farmacéuticamente aceptables del mismo).

Ahora bien, con base en lo anterior y con el ánimo de demostrar el inequívoco carácter novedoso que presenta la materia revelada en el nuevo capítulo reivindicatorio de la presente solicitud de patente frente a las enseñanzas de D1, a continuación me permito presentar las siguientes consideraciones técnicas:

- Tal como se comentó previamente, en la reivindicación 4 del documento D1 se enseña una forma de dosificación que comprende entre aproximadamente 3.5 mg y aproximadamente 200 mg de ibandronato (o una de sus sales o ésteres farmacéuticamente aceptables).

  Contrario a esto, el nuevo capítulo reivindicatorio de la solicitud en cuestión está dirigido a proteger un medicamento que comprende 100 mg ó 150 mg de la sal monosódica del ácido ibandrónico monohidrato.

  De lo anterior queda claro que mientras D1 revela un rango de dosificación (3.5 mg a 200 mg), **en la presente solicitud de patente se protegen dos cantidades específicas de principio activo (100 mg y 150 mg)**, hecho que según las enseñanzas del Manual Andino, constituye un claro e inequívoco factor de novedad de la materia revelada en la solicitud de patente en cuestión (frente a las enseñanzas de D1), toda vez que de acuerdo con las disposiciones establecidas en el mencionado Manual: *"Una expresión general no*

destruye la novedad de un elemento específico que cae dentro de esta expresión".[1]

Adicionalmente, de la cuidadosa lectura de **D1** es claro que en dicha anterioridad no se revelan de manera explícita las cantidades específicas de ibandronato establecidas en la presente solicitud de patente, y debido a que en el Manual Andino de Patentes también se establece que: *"Para determinar la novedad de la invención, se debe comprobar si existen anticipaciones del estado de la técnica que contengan explícitamente todas las características técnicas esenciales de la invención. El examen de novedad se efectúa comparando elemento por elemento de la invención tal como está definido por las reivindicaciones con los del estado de la técnica"*,[2] es absolutamente claro que la materia definida en el nuevo capítulo reivindicatorio presenta un inobjetable carácter novedoso frente a las enseñanzas del documento D1.

- En conexión con lo anterior, resulta de gran importancia resaltar que tanto en algunos apartes de la descripción del documento **D1**, como en las reivindicaciones 7 a 10 de dicha anterioridad, se mencionan cantidades específicas de ibandronato (incluyendo sales ó ésteres del mismo), las cuales, sin embargo, no sólo no corresponden a las cantidades específicamente establecidas en la presente invención, sino que se encuentran marcadamente alejadas. En este sentido, mientras que en D1 se mencionan unidades de dosificación que comprenden 35 mg, 40 mg, 45 mg y 50 mg de ibandronato, la presente solicitud de patente está dirigda a proteger medicamentos que comprenden 100 mg ó 150 mg de ibandronato.

- De otro lado, a partir de una comparación básica entre el capítulo reivindicatorio del documento **D1** y el capítulo reivindicatorio de la presente invención, es claro que mientras la materia protegida en **D1** comprende exclusivamente *métodos* de tratamiento, el capítulo reivindicatorio que se remite junto con el presente memorial se

[1] SECRETARÍA GENERAL DE LA COMUNIDAD ANDINA. *Manual para el Examen de solicitudes de patentes de invención en las Oficinas de Propiedad Industrial de los Países de la Comunidad Andina.* Lima, Perú: 2004; Página: 67.
[2] Ibid, página: 65.

encuentra dirigido únicamente a proteger composiciones farmacéuticas.

En vista de lo anteriormente planteado, atentamente me permito manifestar que **la materia revelada en el nuevo capítulo reivindicatorio de la presente solicitud de patente presenta un inequívoco carácter novedoso con respecto a las enseñanzas del documento D1.**

De otro lado, a partir de la información analizada en el numeral 4 del presente memorial, en referencia a los sorprendentes beneficios mostrados por las composiciones farmacéuticas reveladas en la solicitud de patente en cuestión, así como a partir del cuidadoso análisis de la memoria descriptiva tanto del documento **D1** como de la presente solicitud de patente, es claro que el nuevo capítulo reivindicatorio que se remite junto con el presente memorial presenta un inobjetable carácter inventivo con respecto a las enseñanzas que conforman el estado de la técnica anterior. En este sentido, me permito resaltar las siguientes consideraciones técnicas:

- En primer lugar, el documento **D1** claramente establece un método para inhibir la resorción ósea en mamíferos, el cual comprende la administración oral de un bisfosfonato mediante un régimen seleccionado entre: dosis una vez por semana, dosis dos veces por semana, dosis cada dos semanas y dosis dos veces al mes.

  Sin embargo, **dicha anterioridad no revela y tampoco sugiere un medicamento que comprenda 100 mg ó 150 mg de ibandronato** (ó una sal farmacéuticamente aceptable del mismo) **y que sea administrado como una única dosis mensual**. Ahora, tal como se revela en los anexos A, B y C del presente memorial, dicha diferencia en el régimen de administración del medicamento permite la obtención de marcadas ventajas pues, por un lado, la eficacia terapéutica obtenida mediante las composiciones de la presente solicitud es tan o más alta que la obtenida con las dosificaciones enseñadas en el arte previo; y, por otro lado, la aceptación por parte de las pacientes a un régimen de tratamiento mensual con ibandronato es mucho más alta con respecto a la aceptación dada a un régimen de tratamiento diario, semanal o quincenal, como consecuencia de las implicaciones que dichas formas de dosificación

tienen en los efectos laterales negativos producidos por una administración recurrente de dicho compuesto activo.

- En conexión con lo anterior, resulta de gran importancia resaltar que el documento **D1** no sugiere de manera alguna la posible administración de bisfosfonatos en un régimen mensual, hecho que puede explicarse al tener en cuenta la información revelada en el artículo: *E. Solomon; Ibandronate Treatment for Osteoporosis: Rationale, Preclinical, and Clinical Development of Extended Dosing Regimens"; Current Osteoporosis Reports; 2006; 4 (1); 14-20,* en donde claramente se afirma que previo a la publicación de la presente solicitud de patente se asumía como parte del estado de la técnica que debido a que los osteoclastos tienen una vida media de entre 2 y 3 semanas, éste último rango era el máximo intervalo de tiempo que debía existir entre la administración de bisfosfonatos a un paciente en tratamiento.

En síntesis, atentamente me permito señalar que todo lo anteriormente planteado demuestra el inequívoco carácter novedoso e inventivo que presenta la materia revelada en la presente solicitud de patente con respecto a las enseñanzas del documento **D1**.

6.2 **Consideraciones con respecto al documento D2**

En el artículo científico *"Ibandronate: a comparison of oral daily doping versus intermittent doping in postmenopausal osteoporosis"* básicamente se revela un estudio clínico en el que se comparó la eficacia y seguridad de: 1) una dosificación oral intermitente de ibandronato y, 2) una dosificación oral contínua de ibandronato, en mujeres que padecen osteoporosis postmenopáusica.

De manera específica, en **D2** se revelan los resultados de un estudio clínico en el que se administró una dosis contínua diaria de 2.5 mg de ibandronato a un primer grupo de mujeres, y en el que paralelamente se administró a un segundo grupo de mujeres una dosis intermitente de 20 mg de ibandronato únicamente durante 24 días, seguido por 9 semanas sin la aplicación del medicamento.

Dicho estudio permitió concluir básicamente que los regímenes de administración contínua e intermitente de ibandronato en mujeres que padecen de osteoporosis postmenopáusica generan cambios equivalentes en la densidad mineral y en la renovación ósea.

Ahora bien, a partir de lo planteado previamente puede concluirse que **las enseñanzas del documento D2 tampoco afectan la novedad de la materia revelada en el nuevo capítulo revindicatorio de la presente solicitud de patente, toda vez que en dicha anterioridad de ninguna manera se revela un medicamento que comprenda 100 mg ó 150 mg de un bisfosfonato (o una sal farmacéuticamente aceptable del mismo), junto con excipientes farmacéuticamente aceptables.**

De conformidad con lo anterior, me permito resaltar una vez más que **D2** reporta únicamente un estudio clínico para el tratamiento de la osteoporosis, el cual de ninguna manera incluye la administración a las mujeres que hicieron parte de dicho estudio clínico de un medicamento que comprenda un bisfosfonato en las cantidades definidas dentro de la presente solicitud de patente, esto es, 100 mg ó 150 mg de dicho compuesto activo.

De otro lado, con respecto al salto inventivo logrado en el estado de la técnica por cuenta de la materia revelada en la presente solicitud de patente, con respecto a las enseñanzas del documento D2, resulta de gran importancia tener en cuenta las siguientes consideraciones:

- Por un lado, dicha anterioridad enseña únicamente terapias de tratamiento que incluyen la administración de: 1) dosis diarias de 2.5 mg de ibandronato, ó 2) dosis intermitentes de 20 mg de ibandronato únicamente durante 24 días, seguidos por 9 semanas sin la aplicación del medicamento.

  Sin embargo, **dicha anterioridad no revela y tampoco sugiere un medicamento que comprenda 100 mg ó 150 mg de ibandronato** (ó una sal farmacéuticamente aceptable del mismo) **y que sea administrado como una única dosis mensual**. Ahora, tal como se ha comentado previamente en el presente memorial, dichas modificaciones tanto en la cantidad de dosis de bisfosfonatos, como

en el régimen de administración, implica la obtención de sorprendentes ventajas terapéuticas, las cuales de ninguna manera habrían podido ser sugeridas por una persona versada en la materia en cuestión, puesto que antes de los estudios experimentales que condujeron a obtener la información revelada en la presente solicitud de patente se asumía como parte del estado de la técnica que debido a que los osteoclastos tienen una vida media de entre 2 y 3 semanas, éste último rango era el máximo intervalo de tiempo que debía existir entre la administración de bisfosfonatos a un paciente en tratamiento (Ver anexo B).

- Aparte de lo anterior, resulta de gran importancia resaltar que las características técnicas del novedoso medicamento revelado en la presente solicitud de patente tampoco pueden considerarse obvias y/o lógicas por una persona experta en la materia si se tiene en cuenta que una composición farmacéutica que comprenda 100 mg ó 150 mg de ibandronato para administración mensual, ni siquiera corresponde a la simple suma de las treinta dosis diarias de ibandronato sugeridas en el estado de la técnica. En este sentido, por ejemplo, según las enseñanzas de **D2** la dosis diaria corresponde a 2.5 mg, lo cual significa que un paciente tratado bajo ese régimen de administración consumiría tan sólo 75 mg mensuales de ibandronato. Como puede notarse, las características técnicas del medicamento revelado en la presente solicitud de patente implican la administración de el 120% ó el 200% de la dosis de ibandronato sugerida por el estado de la técnica. Sin embargo, sorprendentemente se ha encontrado que dichas dosis ofrecen mayores ventajas para el paciente, tanto en una notable reducción en fracturas, como en comodidad y aceptación.

En vista de lo planteado previamente, atentamente me permito manifestar que las enseñanzas del documento D2 tampoco afectan la novedad y el nivel inventivo de la materia revelada en el nuevo capítulo reivindicatorio de la presente solicitud de patente.

6.3 **Consideraciones con respecto al documento D3**

En términos generales, el documento **WO 9739755** enseña composiciones farmacéuticas para aplicación oral que contienen ibandronato o una sal fisiológicamente tolerable del mismo.

De acuerdo a los autores de dicho documento cada forma de administración de dichas composiciones consiste de una sección interior que contiene el ingrediente activo, la cual está rodeada por un revestimiento libre de ingrediente activo, lo cual permite que éste último sea liberado rápidamente.

Ahora bien, de lo anterior es claro que dicho documento D3 únicamente se limita a enseñar de manera general composiciones de ácido ibandrónico para administración oral. Por lo tanto, es claro que tal anterioridad NO indica de manera alguna la cantidad de ibandronato contenida en la sección interior de dichas composiciones farmacéuticas.

Con base en lo anterior, es decir, debido a que en **D3** de ninguna manera se revela un medicamento que comprenda 100 mg ó 150 mg de un bisfosfonato (o una sal farmacéuticamente aceptable del mismo), junto con excipientes farmacéuticamente aceptables, es claro que la materia revelada en el nuevo capítulo reivindicatorio de la solicitud de patente en cuestión presenta un inobjetable carácter novedoso frente a las enseñanzas del documento D3.

Aparte de lo anterior, del atento análisis de la información revelada en el documento **D3** es posible concluir adicionalmente que dicha anterioridad no afecta de manera alguna el carácter inventivo de la materia revelada en la presente solicitud de patente, toda vez que una persona experta en la materia técnica en cuestión no encuentra en **D3** enseñanza alguna que le sugiera un medicamento de administración mensual que comprenda 100 ó 150 mg de ibandronato (o una sal farmacéuticamente aceptable del mismo) junto con excipientes farmacéuticamente aceptables. Asimismo, es claro que la persona experta en la materia tampoco encontraría obvio el medicamento de la solicitud de patente en cuestión, debido a que éste no habría podido sugerir las notables ventajas técnicas y terapéuticas obtenidas a partir de dicha novedosa composición, tal como se ha comentado previamente en el presente memorial.

7. **CONCLUSIÓN**

En virtud de todo lo anterior, atentamente me permito señalar ante ese Despacho que de conformidad con las drásticas modificaciones realizadas en el capítulo reivindicatorio de la presente solicitud de patente, así como con base en la información y los argumentos técnicos presentados para demostrar el inequívoco carácter novedoso y el sorprendente aporte al estado de la técnica brindado por la materia revelada en dicha solicitud, es completamente claro que se han superado las objeciones expuestas por el señor Examinador, y por lo tanto, dicha solicitud es merecedora del privilegio de patente solicitado.

8. Anexo al presente memorial me permito presentar:

(a) Recibo número 08-44,778, expedido por la Superintendencia de Industria y Comercio, que acredita el pago de las modificaciones mencionadas;

(b) Copia del nuevo capítulo reivindicatorio compuesto por seis (6) reivindicaciones, que reemplaza al Capítulo Reivindicatorio originalmente presentado y en el cual se han realizado las modificaciones anteriormente mencionadas;

(c) Anexo A: E. Solomon; "Ibandronate Treatment for Osteoporosis: Rationale, Preclinical, and Clinical Development of Extended Dosing Regimens"; *Current Osteoporosis Reports; 2006; 4 (1); 14-20;*

(d) *Anexo B: Once monthly dosing increases the proportion of patients who respond to oral ibandronate: 1-year results from MOBILE; J. Bone Miner. Res.; Res 2004; 19 (Suppl. 1):S447 (Abstract M432); y*

(e) Anexo C: Monthly oral ibandronate significantly reduces bone resorption in postmenopausal osteoporosis: 1-year results from MOBILE; J. Bone Miner. Res.; 2004; 19 (Suppl.1):S94 (Abstract F406);

9. En vista de lo anterior, ruego a usted proceder a estudiar nuevamente la solicitud a la luz de las argumentaciones presentadas y conceder el privilegio de patente solicitado.

Señor Superintendente,

ALICIA LLOREDA RICAURTE

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 44,778
FECHA : JUNIO 5 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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***** C O N S I G N A C I O N *****

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LLOREDA Y CIA S. A	CONSIGNACION	BANCO DE BOGOTA	062754307	2756091	05/06/2008	6,040,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-03 CAMBIO DE MODALIDAD Y MODIFICA	12 MARCAS Y LEMAS COMERCIALES		103,000.00
		TOTAL :	$	103,000.00

SON: CIENTO TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

REIVINDICACIONES

1. Un medicamento administrado mensualmente de manera oral, caracterizado porque comprende 100 mg ó 150 mg de un ácido bisfosfónico o una sal farmacéuticamente aceptable del mismo, y uno o más excipientes farmacéuticamente aceptables.

2. El medicamento de la reivindicación 1, en donde el ácido bisfosfónico es el ácido ibandrónico o una sal farmacéuticamente aceptable del mismo.

3. El medicamento de las reivindicaciones 1 y 2, el cual comprende 100 mg de ácido bisfosfónico o una sal farmacéuticamente aceptable del mismo.

4. El medicamento de las reivindicaciones 1 y 2, el cual comprende 150 mg de ácido bisfosfónico o una sal farmacéuticamente aceptable del mismo.

5. El medicamento de acuerdo con cualquiera de las reivindicaciones 1 a 4, en donde el ácido bisfosfónico o la sal farmacéuticamente aceptable del mismo es la sal monosódica del ácido ibandrónico, monohidrato.

6. El medicamento de acuerdo con cualquiera de las reivindicaciones 1 a 5, caracterizado porque es un comprimido recubierto por una película, y en donde el núcleo del comprimido comprende:

- 100 mg o 150 mg de un ácido bisfosfónico o una sal farmacéuticamente aceptable del mismo, de acuerdo con cualquiera de las reivindicaciones 1 a 5;

- Uno o más excipientes farmacéuticamente aceptables seleccionados del grupo conformado por: lactosa, polivinilpirrolidona, celulosa microcristalina, crospovidona, ácido esteárico y dióxido de silicio; Y,

- Uno o más excipientes farmacéuticamente aceptables seleccionados del grupo conformado por: hidroxipropil metilcelulosa, óxido de titanio, talco y polietilenglicol 6000.

Ibandronate Treatment for Osteoporosis: Rationale, Preclinical, and Clinical Development of Extended Dosing Regimens

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Ibandronate is a potent nitrogen-containing bisphosphonate available as a once-monthly oral formulation for the treatment and prevention of osteoporosis. Preclinical experiments with estrogen-depleted rats, dogs, and monkeys demonstrated the efficacy of daily and intermittent ibandronate dosing. Initial clinical trials explored the optimal dosing regimens for oral administration in humans. The Oral Ibandronate Osteoporosis Vertebral Fracture Trial in North America and Europe (BONE) and Monthly Oral Ibandronate in Ladies (MOBILE) trials demonstrated that long-term daily and intermittent administration of ibandronate was efficacious for increasing bone mineral density, reducing markers of bone turnover, and preventing fractures, while maintaining bone quality. These preclinical and clinical ibandronate trials provided progressive evidence that a simple, long interval dosing regimen could offer efficacy and safety comparable with currently available bisphosphonates. It is anticipated that once-monthly ibandronate may have a positive impact on patient adherence, and ultimately, on fracture protection in osteoporotic women.

Introduction

Bone mass is maintained as part of a balance between bone formation and resorption. In patients with postmenopausal osteoporosis (PMO), resorption exceeds formation, resulting in reduced bone mass and a deterioration of bone microarchitecture. Bisphosphonates, at clinically relevant doses, have been shown to reduce the rate of bone loss, increase bone mineral density (BMD), and reduce fracture risk [1].

The chemical structure of bisphosphonates is similar to that of inorganic pyrophosphate; however, bisphosphonates have a phosphorous-carbon-phosphorous backbone. Their high affinity for bone is due to a hydroxyl group at the R^1 position that binds to Ca^{2+} ions in hydroxyapatite bone mineral surfaces at sites of osteoclast activity [2]. The antiresorptive potency of individual bisphosphonates is determined by their R^2 side chain constituents [3].

Radio-labeled molecules were used to demonstrate that bisphosphonates are internalized by osteoclasts [4,5]. Once inside the osteoclasts, bisphosphonates containing nitrogen in the moiety at the R^2 position inhibit osteoclast function predominantly through inhibition of farnesyl pyrophosphate (FPP) synthase, an enzyme of the mevalonate pathway [2]. Inhibition of FPP synthase prevents prenylation of small GTPases such as members of the Ras, Rho, Rab, Rac, and Cdc42 subfamilies [2]. This, in turn, disrupts a variety of cell processes important for osteoclast function, including cytoskeletal rearrangement, membrane ruffling, and intracellular vesicle trafficking, resulting in osteoclast apoptosis [2,6]. Osteoclast apoptosis is not necessary for inhibition of bone resorption [7•]. Bisphosphonates also affect bone formation, mainly through reduction of activation frequency, as evidenced by a reduction in bone formation surfaces [8–10], but this occurs to a lesser extent than resorption [1]. The net result of bisphosphonate administration is a gain in BMD.

The duration of bisphosphonate action is dependent on a combination of factors, notably potency, dose, dosing interval, and bone turnover rate [11••]. It has been proposed that differences in the degree to which a bisphosphonate binds to bone are responsible for the varying persistence of its skeletal actions, affecting potency and duration of action [11••,12]. However, this may not be the case and the potency of inhibition of the FPP synthase system is considered to be a predominant

factor [2,13]. To facilitate intermittent dosing, a bisphosphonate must be biologically active in sufficient quantity to inhibit bone turnover for the entire between-dose interval and potent enough to maintain dosing within a range that is well tolerated but still effective [14].

Ibandronate is a highly potent, nitrogen-containing bisphosphonate. The tertiary nitrogen group in the R^2 side chain position, coupled with the hydroxyl group in its R^1 lateral chain, renders ibandronate approximately two-fold, 10-fold, 50-fold, and 500-fold more potent than risedronate, alendronate, pamidronate, and clodronate, respectively, as measured by bone resorption inhibitory activity in the arotinoid assay in rats [15]. As mentioned previously, potency is an important factor in the development of simplified dosing regimens with extended between-dose intervals. In this paper the preclinical evidence for extended dosing along with recently published clinical trial data in which the therapeutic advantages of ibandronate, hypothesized during the drug development process will be reviewed.

Preclinical Data

The World Health Organization has acknowledged the value of preclinical studies in the development of osteoporosis drugs [16]. Currently available bisphosphonates, notably alendronate, risedronate, and zoledronate, have been extensively tested in animal models [8,17–25]. In ovariectomized rats and nonhuman primates, these agents were shown to prevent bone turnover, while increasing BMD [8,17–21]. Studies in dogs have been used to examine micro-damage accumulation and have shown that long-term administration with pharmacologic doses of these compounds does not negatively affect bone quality [22–25].

Ibandronate efficacy has been demonstrated in four animal models, rat, dog, monkey, and mini-pig (not included in this review). Food and Drug Administration (FDA) guidelines recommend that agents for the prevention or treatment of osteoporosis be tested in two different species, the ovariectomized rat and a second non-rat model [26]. Ovariectomized rats are utilized because the bone loss observed in this animal model is similar to that experienced by postmenopausal women [27]. In both groups, there is an increase in bone turnover rate, with an initial phase of rapid bone loss followed-up by a period with a marked decrease, a higher degree of loss of cancellous versus cortical bone, and a decrease in calcium absorption [27]. Both rats and humans respond to treatment with estrogen therapy, tamoxifen, bisphosphonates, parathyroid hormone, calcitonin, vitamin D, and exercise [27]. The main difference between the two species is that rats do not undergo menopause during mid-life followed-up by a period of accelerated bone loss [27]. In addition, aged ovariectomized rats 8 months or older are a more appropriate model of PMO than younger, actively growing rats. By using older rats, ibandronate studies eliminated potential confounding factors, including bones that are still actively growing and age-dependent metabolic activities [28•].

In an initial dose-ranging study, 8-month old ovariectomized or sham-operated rats were treated immediately after surgery with daily ibandronate in doses from 0.1 to 30.0 μg/kg or vehicle. Ibandronate dose-dependently inhibited bone loss, as measured by changes in the radiographic density of the proximal metaphyses of the tibias [28•]. The optimal dose (the lowest dose that was not significantly different from the sham-operated solvent control) was 1 μg/kg/d [28•]. Administering a loading dose to attain an immediate steady-state level of drug, did not affect the results [28•].

In an extension of the study described above, varying treatment regimens were administered over a period of 20 to 22 weeks, such that the total cumulative dose per ovariectomized animal equaled 154 μg/kg [28•]. The between-treatment intervals were derived by taking into account the bone remodeling time in rats and findings that the effects of a single dose of ibandronate lasted 2 to 3 weeks in a model of retinoid-stimulated bone destruction [15]. The therapy-free intervals were chosen to be one, two, or three times the length of the bone turnover cycle in rats [28•]. Animals received 1 week "on" treatment, followed-up by a therapy-free interval of 2, 4, or 6 weeks [28•]. After completing the required number of cycles, the rats received an additional week "on" treatment. The radiographic densities of femurs from all groups of treated animals remained equivalent to those of sham-operated controls [28•]. This pivotal study demonstrated that the interval between doses could exceed estimated bone turnover time while maintaining efficacy.

In a follow-up study, 8-month old ovariectomized or sham-operated rats were treated, 10 weeks after surgery, with daily subcutaneous ibandronate (0.2 to 25 μg/kg) or intermittent ibandronate (25 or 125 μg/kg every 25 days) for 12 months [29]. The 10-week post-surgery interval allowed for substantial bone loss to accumulate prior to treatment. Concentrations of ibandronate in bone were linear with respect to dose, suggesting linear kinetics within the range administered. The skeletal uptake of ibandronate was related to total dose, regardless of administration schedule. Dose-dependent increases were seen in BMD, trabecular bone volume and trabecular number, load to failure, and yield loads in long bones and vertebrae [29].

As part of a long-term safety study, 6-week old female and male Wistar rats were given vehicle or 3, 7, or 15 mg/kg/d of ibandronate orally by gavage for 104 weeks. Compressive strength, BMD, and stiffness were significantly higher in ibandronate-treated versus vehicle-treated rats [30]. The doses of ibandronate given to the rats in this study far exceeded doses given in earlier studies to simulate long-term therapy. Lifelong administration of ibandronate increased BMD and maintained or improved bone quality [30].

Concerns have been discussed relating to long-term administration of bisphosphonates and the theoretic possibility the chronic reductions in bone turnover may result in accumulation of micro-fractures, normally repaired by bone remodeling, which could cause bone fatigue fractures [31]. Evidence supporting this concept was reported in a study involving long-term administration of etidronate in dogs [10]. In contrast, the ibandronate safety study in rats found significant increases in ultimate load and stress values with long-term ibandronate treatment [30]. The results indicate that micro-fracture accumulation and reduced compressive strength of vertebral bodies did not occur in the rat preclinical trials [30].

In addition to rats, dose-response osteoporosis prevention studies with ibandronate were performed in dogs. Ovariohysterectomized (OHX) dogs were injected subcutaneously with vehicle or ibandronate doses ranging from 0.1 to 100 μg/kg/d for 1 month [32]. The dogs given vehicle exhibited a significant decrease in bone volume within 1 month of OHX surgery [32]. Ibandronate, in doses of greater than or equal to 1 μg/kg/d, was required to prevent bone loss [32]. No adverse effects on bone structure, formation, or resorption were seen in sham-operated dogs receiving ibandronate at doses of 1 μg/kg/d [32].

In a second study that examined osteoporosis treatment in dogs, ibandronate was administered daily and intermittently for 1 year to OHX dogs 4 months after surgery (to allow for development of bone loss) [33]. Dogs on the intermittent ibandronate dosing regimen received the same cumulative dose as dogs receiving the highest continuous daily dose (3640 μg/kg/d) [33]. Dogs were monitored for 12 months after initiation of treatment. Ibandronate (14 μg/kg/d or intermittently dosed) completely reversed bone loss, as measured by bone volume, to levels similar to baseline values [33]. Intermittent dosing in this study did not significantly reduce or suppress bone turnover as determined by histomorphometry and bone mineral properties as measured by Fourier-transform infrared macrospectroscopy [33]. It was theorized that the 65 μg/kg/d intermittent dose would be sufficiently potent to suppress bone resorption while allowing more bone to form during the treatment-free periods [33].

In a study using a dog model developed to simulate fracture repair, 24-month old dogs received daily ibandronate, intermittent dosing of ibandronate with 2- to 6-week, dose-free intervals, or vehicle for 36 weeks [34]. Animals in the active dosing regimens all received the same total dose of ibandronate over the entire treatment period (252 μg/kg over 36 weeks) [34]. In week 27 or 28, tiny holes were drilled in the left tibia, and a bone marrow ablation was performed on the ipsilateral femur [34]. Ibandronate administration did not quantitatively or qualitatively affect the initial stage of bone repair healing and it did not affect the activation of cortical remodeling that occurs during the second stage of fracture healing [34].

Ibandronate was tested further in non-human primates, which are the most similar to humans as they have similar reproductive hormone patterns and menstrual cycles. Ovariectomized monkeys are considered the best model for studying the efficacy of anti-osteoporotic drugs [16]. After ovariectomies, cynomolgus monkeys exhibit changes in bone mass and turnover similar to what is observed in postmenopausal women [35,36].

In dose-ranging osteoporosis prevention studies in monkeys, 66 ovariectomized or sham-operated monkeys were given intravenous bolus injections of placebo or 10, 30, or 150 μg/kg of ibandronate at 30-day intervals for 16 months [16,37,38]. Doses were chosen based on the rat and dog studies and were meant to represent a suboptimal dose, the optimal effective dose, and five times the optimal dose [38]. Suboptimal dosing (10 μg/kg) of ibandronate only partially prevented OVX-induced effects [37]. Thirty μg/kg of ibandronate prevented osteopenia, while 150 μg/kg of ibandronate increased bone mass (measured by dual-energy x-ray absorptiometry [DXA] bone densitometry) and improved bone strength at the spine and femoral neck (measured by biomechanical testing of lumbar vertebrae—compression, whole ulnae in 3-point bending, and femoral neck strength), without having a negative effect on bone quality [37].

This was the first non-human primate study to use a bisphosphonate dosing schedule resembling a clinical regimen [11••,37]. Consequently, clinical trials with bolus intravenous administration of ibandronate every 3 months were initiated [39]. Data from monkeys were consistent with results obtained in phase II clinical trials [37–39]. Intravenous bolus injections of ibandronate every 3 months increased lumbar spine BMD by 5.2% after 12 months in postmenopausal women (2 mg) and approximately 4% in monkeys (eight monthly doses of 150 μg/kg/dose) [37,39].

Overall, the results from animal studies indicated that oral gavage, subcutaneous, or intravenous administration of ibandronate with extended dosing intervals reduced bone turnover, increased BMD, and maintained bone quality. Findings with all three species were consistent—ibandronate had a dose-dependent effect on BMD in estrogen-depleted animals. The optimal dose of ibandronate in rats, dogs, and monkeys was 1 μg/kg/d administered subcutaneously [28•,32,33,37].

Preclinical studies also demonstrated that bone quality was maintained with long-term administration of ibandronate, [30,33,34,37] a finding that is necessary for long-term safety. In rats receiving ibandronate for 104 weeks, bone quality was maintained or improved [30]. In both studies of OHX dogs receiving daily or intermittent ibandronate for 1 year and ovariectomized monkeys treated with monthly injections of ibandronate for 16 months, histomorphometric analyses demonstrated that bone structure remained normal [33,37]. The demonstrated efficacy of ibandronate for the prevention and

treatment of osteoporosis in animal models, coupled with maintenance of bone quality, provided the basis for the development of intermittent dosing regimens in clinical trials.

Phase I and II Studies

Phase I and II trials were aimed at determining the optimal dose and dosing frequency. Based on initial tests in rats comparing ibandronate with other bisphosphonates, the predicted active dose of ibandronate in humans was estimated to be approximately 0.8 to 1.0 mg/day [15].

The estimated range was expanded, and a placebo-controlled, dose-finding study was performed in which women received ibandronate in doses from 0.25 to 5.0 mg/d for 12 months [40]. Ibandronate 2.5 mg/d was determined to be the most effective dose (similar treatment effects were observed in patients receiving 5.0 mg/d) [40]. Oral daily ibandronate reduced bone turnover markers, increased total body bone mineral content, and significantly increased BMD at the lumbar spine, total proximal femur, trochanter, and femoral neck [40].

Similar results were seen in a separate study in which daily dosing was compared with intermittent dosing (2.5 mg of oral ibandronate daily or 20 mg oral ibandronate every other day for the first 24 days out of every 3 months) [41]. Significant reductions in bone markers of resorption and formation were observed and maintained throughout the study [41]. Daily and intermittent dosing led to similar numeric increases in BMD at the lumbar spine, total hip, trochanter, and femoral neck after 2 years [41].

A review of three ibandronate phase II studies noted that the efficacy achieved with ibandronate was similar regardless of treatment regimen, whether administered orally 2.5 mg daily, orally 20 mg every other day for 12 doses every 3 months, or intravenously once every 3 months [42]. There were comparable increases in BMD and significant reductions in biochemical markers of bone turnover with all three regimens tested [39–41].

Findings in phase I and II clinical trials served as the basis for the development of phase III studies such as the Oral Ibandronate Osteoporosis Vertebral Fracture Trial in North America and Europe (BONE) and the Monthly Oral Ibandronate in Ladies (MOBILE) trials, which evaluated daily and intermittent dosing ibandronate regimens in postmenopausal women.

BONE Study

The BONE trial was a 3-year, randomized, double-blind, placebo-controlled, parallel-group study, and the only ibandronate trial to date with a fracture endpoint. Postmenopausal women (n = 2946) with a BMD T-score of -2.0 to -5.0 in at least one vertebra (L1-L4) and one to four prevalent vertebral fractures (T4-L4) received placebo or oral ibandronate 2.5 mg daily or 20 mg every other day for 12 doses every 3 months [43•]. The primary endpoint of the study was the rate of new morphometric fractures with 3 years of treatment. Secondary measures included the rate of new or worsening vertebral fractures, clinical vertebral fractures, and clinical osteoporotic nonvertebral fractures, BMD changes at the lumbar spine and proximal femur, changes in levels of bone resorption and formation markers, and changes in height [43•].

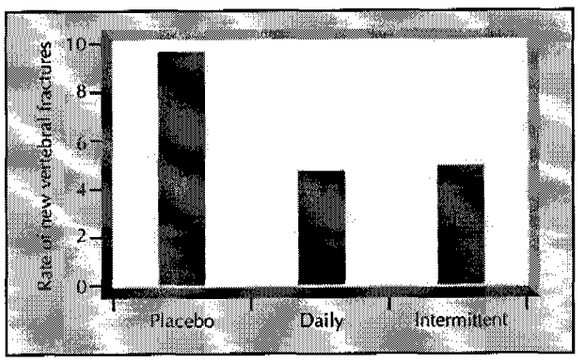


Figure 1. BONE study: incidence of new vertebral fractures after 3 years for patients dosed with daily and intermittent ibandronate and placebo.

Rate of new vertebral fractures was reduced in patients taking daily ibandronate (4.7%) and intermittent ibandronate (4.9%), compared with placebo (9.6%) (Fig. 1) [43•]. This corresponds to a reduction in the risk for new vertebral fractures of 52% (P = 0.0001) and 50% (P = 0.0006) for daily and intermittent dosing, respectively [43•]. Reductions in the incidence rates of new clinical vertebral fractures were 2.8% for daily and intermittent ibandronate dosing, compared with 5.3% for the placebo group [43•]; relative risk reduction of 49% for daily dosing, and 48% for intermittent dosing [43•]. In a post hoc analysis, it was determined that in higher-risk patients (baseline femoral neck BMD T-score of < -3.0), there was a reduction in the relative risk for nonvertebral fractures of 69% (P = 0.013) and 37% (P = 0.22) for daily and intermittent dosing, respectively. Significantly more height loss was observed in patients receiving placebo (5.6 mm) versus 3.9 mm (P = 0.0005) for daily and 4.7 mm (P = 0.0144) for intermittent dosing. Increases in lumbar spine BMD of 6.5%, 5.7%, and 1.3% were observed for daily, intermittent dosing, and placebo, respectively [43•]. Total hip BMD increased by 3.4% and 2.9% in the daily and intermittent dosing groups, respectively, while there was a net loss of 0.7% in the placebo group [43•]. Femoral neck BMD was increased by 2.8% and 2.4% in the daily and intermittent dosing groups, respectively, with a net loss of 0.6% in the placebo group [43•]. Trochanter BMD increased by 5.5%, 5.2%, and 0.2% in the daily, intermittent, and placebo groups, respectively [43•].

Within 3 months and throughout the 3-year study, there were significant reductions in bone resorption and

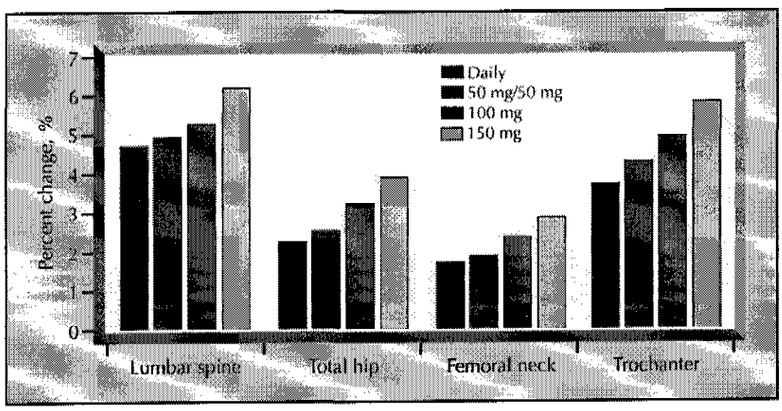


Figure 2. MOBILE study: changes from baseline in lumbar spine bone mineral density for patients treated with daily and intermittent ibandronate at 2 years.

formation markers in patients on both ibandronate treatment regimens versus placebo. C-telopeptide of type I collagen (CTX)/creatinine and N-telopeptide of type I collagen (NTX)/creatinine were reduced by 65.3% and 68.3% in the daily dosing group and 52.7% and 59.2% in the intermittent dosing group ($P < 0.001$ for both groups vs the placebo group) [44]. Levels of osteocalcin were reduced by 35.8% in the daily dosing group and 40.9% in the intermittent dosing group versus 2.1% in the placebo group ($P < 0.001$ for both ibandronate groups) [44].

A histomorphometric evaluation of a subgroup of patients from the BONE study assessed bone quality and architecture [45]. Patients underwent a transiliac bone biopsy at month 22 or 34 of treatment. In all cases, newly formed trabecular bone retained its structure with no indications of woven bone, marrow fibrosis, or signs of cellular toxicity [45]. A qualitative assessment found no impairment in bone matrix mineralization [45].

The BONE clinical trial demonstrated for the first time that significant fracture efficacy could be achieved with an intermittently administered bisphosphonate. While the study demonstrated that intermittent dosing was possible, the dosing regimen used in the study was not practical. The MOBILE study was initiated to examine efficacy with a more simplified dosing regimen (once monthly).

MOBILE Study

The MOBILE trial was a 2-year, randomized, double-blind, parallel-group, noninferiority, phase III ibandronate study and was the first bisphosphonate trial to evaluate a monthly oral regimen. Postmenopausal women ($n = 1609$) 55 to 80 years of age with osteoporosis (mean lumbar spine [L2-L4] BMD T-scores of -2.5 to -5.0) were included. Baseline assessments for the presence of vertebral fractures were not performed in this trial.

Upon enrollment, participants were randomized to one of four ibandronate treatment groups—2.5 mg daily, 50+50 mg once-monthly (50-mg dose given for 2 consecutive days), 100 mg once-monthly, and 150 mg once-monthly. Results from this study were analyzed after 1 and 2 years. The primary efficacy endpoint was the percent increase from baseline in lumbar spine BMD, as measured by DXA after 1 year. Secondary endpoints included measurements of BMD of the lumbar spine and proximal femur (total hip, femoral neck, trochanter) at 2 years. This information was used to assess the proportion of patients achieving predefined increases in the lumbar spine and total hip; measurements that have previously been identified as being associated with antifracture efficacy [46,47]. Changes from baseline in serum CTX (sCTX) concentrations were also measured at 3, 6, 12, and 24 months.

After 1 year, lumber spine BMD increased in the daily and monthly dosing groups [48•]. Noninferiority was established, given that the lower boundary of each one-sided 97.5% confidence interval was above the predetermined noninferiority margin for each comparison of a monthly versus the daily dose [48•]. Having demonstrated noninferiority, further testing was performed, which confirmed that the monthly dosing regimens and the 150-mg dose in particular, were superior to daily dosing [48•]. Lumbar spine BMD measurements increased in all treatment groups after 1 year. Numerically greater increases were seen in the once-monthly treatment groups compared with the daily dosing group. The largest increase was seen in patients receiving 150 mg of ibandronate monthly (4.9% vs 3.9% for daily dosing) [48•]. Increases in BMD were also seen in the proximal femur (total hip, femoral neck, trochanter) measurements, with the largest increases seen in the 150-mg dosing group [48•]. Decreases in sCTX were comparable in the daily and once-monthly dosing groups, 67.3% and 75.8% in the daily 2.5- and 150-mg monthly arms, respectively [48•].

Preliminary analyses of data after 2 years confirm the conclusions drawn from the first year's data—monthly ibandronate dosing is at least as effective as daily dosing for the treatment of osteoporosis [48•]. Increases in lumbar spine BMD were observed in the 150-mg once-monthly and daily treatment groups (6.6% and 5.0%, respectively) (Fig. 2) (Reginster, Unpublished data). This represented an increase in BMD from the first year results. Increases in proximal femur BMD (total hip, 4.2% and

2.5%; femoral neck, 3.1% and 1.9%; and trochanter, 6.2% and 4.0% for once-monthly and once-daily, respectively) were also observed. The decreases in sCTX, which were observed after 3 months, were maintained.

Conclusions

The development of extended dosing regimens for ibandronate was achieved through studies progressing from nonprimates, to nonhuman primates, to humans. Animal studies established that it was the cumulative dose of ibandronate, irrespective of dosing regimen, which was related to treatment effectiveness. These studies also demonstrated that bone quality was not compromised with long-term administration. The optimal subcutaneous dose of ibandronate, as determined in animal studies, was the equivalent of 1 μg/kg/d. Adjustments in dosing were made in human studies, which utilized oral administration, to account for the drug's low oral bio-availability.

Phase I and II studies determined the appropriate oral dosing levels and demonstrated the efficacy of ibandronate when administered using various intermittent dosing schedules in humans. Phase III trials, such as BONE and MOBILE, confirmed the long-term efficacy of ibandronate in humans with respect to multiple endpoints, including BMD, bone turnover markers, fracture rates, and bone quality. In the MOBILE study, the optimal dosage for once-monthly administration was determined. Ibandronate (150 mg) is currently the only bisphosphonate approved by the FDA for once-monthly oral dosing for the treatment and prevention of osteoporosis. Ibandronate is the first medication approved for monthly dosing of a chronic condition.

It remains a point of interest to determine the limits of the length of the between-dose interval. Since osteoclasts have a half-life of 2 to 3 weeks, this was believed to be the longest interval possible between bisphosphonate dosing. Studies with ibandronate have demonstrated that the dosing interval can be extended to once-monthly and beyond with maintenance of efficacy. It has been hypothesized that ibandronate released when the bone surface it is deposited on is resorbed may still be pharmacologically active. The limits of the administered doses and between-dose intervals have yet to be determined.

Results from a crossover trial evaluating patient preferences for once-weekly alendronate versus once-monthly ibandronate demonstrated that the majority of patients prefer the once-monthly regimen because it is "easier to follow for a long time" (Emkey, Unpublished data). Given that approximately 50% of patients treated for osteoporosis remain adherent to therapy at 1 year [49,50], strategies must be advanced to support better adherence for women with osteoporosis. While many factors impact adherence to bisphosphonates such as dosing frequency, difficult to tolerate side effects, and complexity of the treatment protocol, it is likely that the reduced medication burden offered by a once-monthly formulation can have a positive impact.

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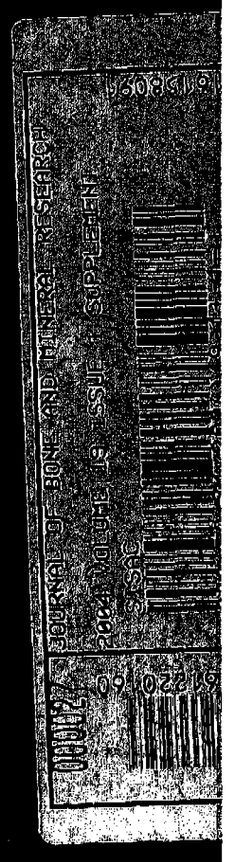
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FL-ALN to specific markers of fluid-phase endocytosis (TRITC-dextran), adsorptive endocytosis (wheat germ agglutinin-TAMRA) and receptor-mediated endocytosis (transferrin-TAMRA). Only TRITC-dextran showed a marked degree of co-localisation with FL-ALN, suggesting that a major component of BP uptake is mediated by fluid-phase endocytosis.

Using flow cytometry, J774 cells were found to markedly accumulate FL-ALN within 4 hours. Consistent with our previous findings, molar excess of the non-N-BP CLO dramatically inhibited the vesicular uptake of 100μM FL-ALN. Co-treatment of J774 cells with FL-ALN and 250μM CLO inhibited uptake of FL-ALN by 90%. This inhibitory effect of CLO was not due to inhibition of fluid-phase endocytosis, since CLO did not affect the uptake of FITC-dextran.

Since BPs are non-hydrolysable analogues of pyrophosphate (PP_i) we hypothesised that PP_i may also compete with BPs for cellular uptake. Co-treatment of J774 cells with 250μM PP_i decreased FL-ALN uptake by 76%. Due to the high affinity of BPs for divalent ions (such as Ca^{2+}), we investigated whether the inhibitory effect of CLO or PP_i was due to Ca^{2+} chelation. Whilst molar excess Ca^{2+} ions stimulated FL-ALN uptake, 500μM EGTA (a Ca^{2+} chelator) inhibited FL-ALN uptake by 96%, which was reversed in the presence of 2mM Ca^{2+}. Supplementation of 250μM CLO or PP_i with molar excess (1mM) Ca^{2+} partially prevented the inhibitory effect of CLO, but not PP_i, on FL-ALN uptake.

These observations show that cellular uptake of BPs can occur by fluid-phase endocytosis. However, there appears to be a specific recognition step prior to endocytosis that is dependent on Ca^{2+} and can be blocked by competition with PP_i or other BPs, such as CLO.

Disclosures: K. Thompson, None.

M431

Fluvastatin Prevents Bisphosphonate-Induced Vγ9Vδ2 T-Cell Activation and Proliferation *In Vitro*. K. Thompson, M. J. Rogers. Medicine & Therapeutics, University of Aberdeen, Aberdeen, United Kingdom.

An acute phase response is the major adverse effect of intravenously-administered nitrogen-containing bisphosphonates (N-BPs) and is associated with the activation (TNFα and IFNγ release) and proliferation of the major subset of γ,δ-T cells in humans ($Vγ9Vδ2^+$ subset). We, and others, have recently reported that the stimulatory effects of N-BPs on γ,δ-T cell proliferation in cultures of human PBMCs are most likely due to inhibition of FPP synthase, an enzyme in the mevalonate pathway. By this mechanism, N-BPs cause the accumulation of upstream isoprenoid lipids such as IPP, which then directly activate $Vγ9Vδ2^+$-T cells. N-BPs, such as zoledronic acid (ZOL), stimulate γ,δ-T cell proliferation in human PBMC cultures with a similar order of potency to the order of potency for inhibition of FPP synthase. Mevastatin, by inhibiting HMG-CoA reductase, can abrogate the stimulatory effects of N-BPs on γ,δ-T cells by preventing the N-BP-induced accumulation of IPP.

Treatment of PBMC cultures with 1μM ZOL for 7 days caused an ~8-fold increase in the proportion of γ,δ-T cells in the $CD3^+$ population. This proliferative effect of ZOL was decreased by >75% when PBMCs were simultaneously treated with 1μM fluvastatin (FLU). Consistent with this, 1μM ZOL caused a marked increase in the proportion of $Vγ9Vδ2^+$-T cells in the γ,δ-T cell population from ~70% (+/-9.1%) in naïve cultures to 98.6% (+/-1.6%) after 7 days treatment. Simultaneous treatment with FLU reduced the ZOL-induced increase in the proportion of $Vγ9Vδ2^+$-T cells to 86% (+/- 2.9%). The inhibitory effect of FLU could be abolished by replenishing cells with mevalonate, suggesting that FLU prevents $Vδ2^+$-T cell proliferation by inhibiting HMG-CoA reductase and preventing ZOL-induced accumulation of IPP.

Although the concentration of ZOL used in this study is similar to the C_{max} following intravenous administration to patients *in vivo* (1μM), plasma concentrations decrease rapidly with a $t_{½}$ of <2hrs. Therefore, the effectiveness of a short pulse of ZOL for inducing IFNγ release in PBMC cultures was investigated. A 2hr pulse of 1μM ZOL induced a 10.3-fold (+/-0.7) increase in IFNγ release from PBMCs after 48hrs. A simultaneous 2hr pulse with 1μM FLU markedly decreased ZOL-induced IFNγ release by >70%. When FLU was present for the entire 48hr period, FLU was only slightly more effective at preventing the ZOL-induced IFNγ release than when present only for the 2hr ZOL pulse, suggesting that sufficient FLU is internalised by PBMCs within a 2hr period to prevent the accumulation of IPP resulting from a clinically relevant exposure to ZOL. Co-administration of FLU with intravenous N-BPs may therefore provide a means for preventing the acute-phase response *in vivo*.

Disclosures: K. Thompson, Novartis Pharma AG 2.

M432

Once Monthly Dosing Increases the Proportion of Patients who Respond to Oral Ibandronate: 1-Year Results from MOBILE. R. Emkey[1], D. Felsenberg[2], J. J. Stepan[3], C. Hughes*[4], E. Dumont*[5], P. Van der Auwera*[4], R. R. Recker[6]. [1]Radiant Research, Wyomissing, PA, USA, [2]Charite - Campus Benjamin Franklin, Berlin, Germany, [3]Charles University, Prague, Czech Republic, [4]F. Hoffmann-La Roche Ltd, Basel, Switzerland, [5]GlaxoSmithKline, Collegeville, PA, USA, [6]Creighton University, Omaha, NE, USA.

Studies of antiresorptive agents indicate that 1-year threshold values for treatment-induced increases in BMD and decreases in BCM predict for antifracture efficacy.[1] Ibandronate (Bonivа®) is a potent, nitrogen-containing BP with antifracture efficacy when given daily or intermittently.[2] A 2-year, randomized, double-blind, phase III, non-inferiority study (MOBILE) is comparing the efficacy and safety of 50/50mg (single doses on consecutive days), 100mg (single day) and 150mg (single day) monthly oral ibandronate with oral daily ibandronate (2.5mg; 3-year vertebral fracture risk reduction: 52%) in 1,609 women with PMO. After 1 year, a prespecified analysis examined the proportion of patients in each arm achieving increases in: lumbar spine (LS) BMD above baseline or 6%; total hip (TH) BMD above baseline or 3%; both LS and TH BMD above baseline. The proportion of patients achieving decreases in sCTX below defined threshold values was also examined.

After 1 year, the majority of patients achieved increases in LS or TH BMD above baseline (**Table**). Compared with the daily arm, significantly more patients achieved increases above baseline in the 150mg arm for LS BMD and the 100mg and 150mg arms for TH BMD. Likewise, more patients in the 100mg and 150mg arms achieved substantial increases in LS BMD (>6%) and TH (>3%) BMD than in the daily arm. In addition, most participants achieved increases in both LS and TH BMD above baseline ($p≤0.001$ for 100mg and 150mg vs 2.5mg). In the analysis of sCTX, a significantly greater proportion of patients in the 150mg arm consistently achieved decreases in sCTX of >30%, >50% and >70%, respectively, compared with the daily arm. In summary, a larger proportion of women receiving 100mg and 150mg monthly oral ibandronate achieve increases in LS and/or TH BMD after 1 year versus those receiving daily ibandronate. Moreover, compared with daily, significantly more patients receiving 150mg ibandronate achieve threshold values for sCTX.

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Table. Proportion (%) of participants considered responders to daily or monthly ibandronate.

Relative change (%) in BMD	Daily ibandronate 2.5mg (n=318)	Monthly ibandronate 50/50mg (n=330)	100mg (n=315)	150mg (n=327)
LS BMD >baseline	84.0	87.8	86.5	91.3*
LS BMD >6%	24.2	30.5	32.2*	35.3*
TH BMD >baseline	76.7	81.9	87.1†	90.0†
TH BMD >3%	34.9	38.0	43.4*	48.4†
LS BMD + TH BMD >baseline	65.7	73.2*	77.7†	83.9†

*p<0.05 vs 2.5mg
†p≤0.001 vs 2.5mg

Disclosures: R. Emkey, F. Hoffmann-La Roche Ltd 2.

M433

Relative Change in Bone Mineral Density Is a Valid Surrogate for Antifracture Efficacy with Ibandronate. S. Epstein[1], H. Huss*[2], K. M. Wilson*[3], R. C. Schimmer[3]. [1]Mt Sinai Medical Center, New York, NY, USA, [2]., Leverkusen, Germany, [3]F. Hoffmann-La Roche Ltd, Basel, Switzerland.

Predefined statistical analyses of the findings from recent antifracture studies of oral and intravenous ibandronate in postmenopausal osteoporosis demonstrate a reduction in risk of vertebral fracture that is significantly associated with improvements in BMD.[1,2] In light of these positive findings, an additional statistical analysis[3] was performed to validate relative change (%) from baseline in BMD as a surrogate marker for predicting 3-year VF RR with ibandronate (using total hip and lumbar spine BMD after 1, 2 and 3 years). The following criteria were used to evaluate surrogacy: (1) BMD is affected by treatment; (2) fracture incidence is affected by treatment; (3) BMD is prognostic for fracture; and (4) the proportion (ρ) of the 3-year antifracture effect explained by relative change (%) from baseline in BMD at each time point. For criteria 1-3, parameter estimates were produced using simple logistic regression models. When the studies were considered separately, findings were variable due to the small sample sizes. However, when the data were pooled, robust findings were reported. Notably, the criteria for surrogacy (outlined above; 1-3) were fulfilled for all analyzed surrogate endpoints for 3-year VF RR (**Table**). In addition, values for ρ (criterion 4) indicated that relative change (%) from baseline in total hip and lumbar spine BMD after 2 and 3 years explained a substantial proportion of the 3-year antifracture effect with ibandronate (**Table**). Importantly, values were similar to those obtained for other widely accepted surrogate endpoints. In summary, while not providing a complete explanation for antifracture efficacy, these findings highlight the utility of using relative change (%) from baseline in total hip and lumbar spine BMD after 2 and 3 years as surrogate markers for 3-year VF RR with ibandronate.

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Table. Proportion of 3-year antifracture effect explained by relative change (%) in BMD

Surrogate	Year	Proportion of antifracture effect explained by surrogate
Relative change (%) from baseline in total hip BMD	1	14%*
	2	24%*
	3	37%*
Relative change (%) from baseline in lumbar spine BMD	1	6%*
	2	23%*
	3	27*

*Endpoints fulfilling criteria for surrogacy

Disclosures: S. Epstein, F. Hoffmann-La Roche Ltd 5.

Once-monthly dosing increases the proportion of patients who respond to oral ibandronate: 1-year results from MOBILE

Anthony D. Whitaker, Barry S. Shenstone, Liz Meadows, C. Dunbabin, R.A. Wimalawansa, Peter D. Miller, Jr.

Radiant Research, Winston-Salem, North Carolina, USA; Osteoporosis Program, Baylor University Medical Center, Dallas, Texas, USA; Cambridge Biostatistics, Cambridge, United Kingdom; Addenbrooke's Hospital, Cambridge University, Cambridge, United Kingdom; Hôpital Cantonal Universitaire, Geneva, Switzerland; Robert Wood Johnson Medical School, Somerset, New Jersey, USA; Colorado Clinical Research, Denver, Colorado, USA

SUMMARY

- Maintaining and increasing bone mineral density (BMD) and normalizing bone resorption levels are important therapeutic objectives in postmenopausal osteoporosis.
- A prospective 'responders' analysis of the findings from the MOBILE study of monthly and daily oral ibandronate (Bonviva™) examined the proportion of patients achieving increases in lumbar spine and/or total hip BMD above baseline and threshold values correlated with antifracture efficacy as secondary efficacy endpoints (6% and 3%, respectively).
- A post-hoc analysis also considered the proportion of patients achieving clinically relevant threshold values for median change (%) from baseline in serum CTX (sCTX).
- Versus the daily arm, significantly more patients achieved increases above baseline in the
  - 150mg arm for lumbar spine BMD
  - 150mg and 100mg arms for total hip BMD
  - 150mg and 100mg arms for the combined endpoints.
- A greater proportion of patients in the 150mg and 100mg arms also achieved more substantial increases in lumbar spine BMD (>6%) and total hip BMD (>3%) than in the daily arm.
- With respect to sCTX, the majority of patients achieved decreases of >30% and >50%, and a substantial proportion achieved decreases of >70%
  - as for the BMD endpoints, a significantly larger proportion of patients in the 150mg arm achieved predefined threshold values than in the daily arm.
- Overall, these findings demonstrate that the majority of patients achieve clinically meaningful responses to both monthly and daily oral ibandronate therapy.
- However, compared with daily dosing, a greater proportion of patients receiving once-monthly ibandronate achieve positive therapeutic outcomes.

INTRODUCTION

- Baseline levels of BMD and biochemical markers of bone turnover are strongly predictive of fracture risk in postmenopausal osteoporosis.[1]
- Likewise, antiresorptive treatment-related increases in BMD and decreases in biochemical markers of bone turnover are predictive of vertebral[2] and non-vertebral[3] antifracture efficacy.
- Ibandronate, a potent, nitrogen-containing bisphosphonate, is proven to substantially increase BMD, decrease bone turnover and reduce fracture risk in postmenopausal osteoporosis when administered daily or intermittently (between-dose interval >2 months) as an oral medication.[4]
- The equivalent efficacy and comparable safety profile of monthly and daily oral ibandronate regimens was also recently demonstrated in the MOBILE study.[5,6]
- A predefined 'responders' analysis of the MOBILE study examined the proportion of patients in the monthly and daily treatment arms achieving gains in lumbar spine and/or total hip BMD above baseline and threshold values correlated with antifracture efficacy as secondary efficacy endpoints (6% and 3%, respectively).[7]
- A post-hoc analysis also considered the proportion of patients achieving predefined and clinically relevant levels of sCTX suppression.[8]
- The findings of these analyses are reported below.

METHODS

Study design

- Multinational, double-blind, randomized, phase III, non-inferiority study.
- Women (aged 55–80 years; ≥5 years since menopause [YSM]) with postmenopausal osteoporosis (lumbar spine [L2–L4] BMD T-score <–2.5 and ≥–5).
- 2.5mg daily oral ibandronate, or 50/50mg (single doses on consecutive days), 100mg (single day) or 150mg (single day) monthly oral ibandronate.
- Study medication taken after an overnight fast, immediately upon rising and 1 hour before food, non-study medications and fluids other than water.
- Daily calcium (500mg) and vitamin D (400IU) supplements were provided.

Study endpoints

- The proportion of patients achieving mean increases in lumbar spine BMD above baseline and 6%, total hip BMD above baseline and 3%, and lumbar spine and total hip BMD above baseline after 1 year was a secondary efficacy endpoint.
- The proportion of participants achieving median decreases in sCTX of >30%, >50% and >70% was also explored.

Statistical analysis

- The per-protocol (PP) population was the primary analysis population for all efficacy endpoints.
- Participants were excluded from the PP analysis in the event of: a biased BMD assessment, a baseline T-score >–2.5, an infringement of one of the study exclusion criteria, poor compliance with treatment, or an unconfirmed menopausal status.

RESULTS

Patient characteristics

- In total, 1,609 women participated in the study.
- Of these women, 1,290 fulfilled the criteria for inclusion in the PP analysis (**Table 1**).
- Baseline characteristics were well balanced (**Table 1**).

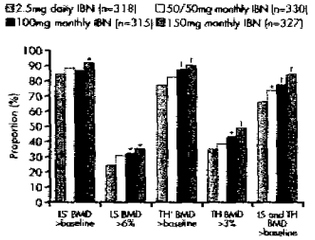
Table 1. **Patient demographics (mean; PP).**

	Dose			
	2.5mg (n=318)	50/50mg (n=330)	100mg (n=315)	150mg (n=327)
Age (years)	65	66	66	66
Weight (kg)	64	63	64	64
Height (cm)	157	157	158	158
Body mass index (kg/m²)	26	26	26	26
YSM (years)	18	18	18	18
History of previous fractures (%)	156 [49.4]	149 [45.2]	144 [45.7]	151 [46.2]
Lumbar spine [L2–L4] BMD (T-score)	–3.3	–3.3	–3.3	–3.3
Total hip BMD (T-score)	–1.8	–1.8	–1.8	–1.8
sCTX (ng/mL)*	0.485	0.520	0.510	0.500
BAP (ng/mL)*	10.545	11.080	11.445	11.520
25-OH-D (ng/mL)	25.6	24.4	25.2	24.7

*Median values

BMD responders analysis

- The findings from the prospectively defined BMD responders analysis are presented in **Figure 1**.
- After 1 year, the majority of patients achieved lumbar spine or total hip BMD gains above baseline.



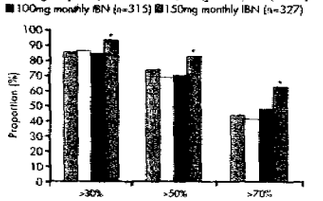
*p<0.05 vs 2.5mg; †p≤0.001 vs 2.5mg; ‡LS = lumbar spine; TH = total hip

Figure 1. **Proportion of participants achieving predefined threshold values for mean change (%) from baseline in lumbar spine and total hip BMD (PP).**

- However, compared with the daily arm, significantly more patients achieved increases above baseline in the
  - 150mg arm for lumbar spine BMD
  - 150mg and 100mg monthly arms for total hip BMD.
- In addition, versus the daily arm, significantly more patients in the 150mg and 100mg monthly arms achieved substantial increases in BMD at the lumbar spine (>6%) and total hip (>3%).
- Moreover, significantly more patients in the 150mg and 100mg monthly ibandronate arms achieved gains in both lumbar spine and total hip BMD above baseline (ps≤0.001 vs daily ibandronate).

sCTX responders analysis

- The proportion of patients achieving decreases in sCTX of >30%, >50% and >70% is presented in **Figure 2**.
- After 1 year, the majority of participants achieved decreases in sCTX of >30% and >50% (**Figure 2**).
- A substantial proportion of participants also achieved decreases in sCTX of >70% (**Figure 2**).
- Compared with the daily regimen, a significantly greater proportion of participants in the 150mg arm achieved decreases in sCTX of >30%, >50% and >70%.



*p<0.05 vs 2.5mg

Figure 2. **Proportion of participants achieving predefined threshold values for mean change (%) from baseline in sCTX (PP).**

CONCLUSIONS

- These findings demonstrate that the majority of patients achieve clinically meaningful responses to monthly and daily oral ibandronate therapy
  - most patients achieve substantial gains in BMD
  - the majority of patients achieve substantial decreases in sCTX.
- Moreover, compared with the daily oral regimen, the proportion of patients achieving positive therapeutic outcomes is significantly greater with monthly oral ibandronate.

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Monthly Oral Ibandronate Significantly Reduces Bone Resorption in Postmenopausal Osteoporosis: 1-Year Results from MOBILE. R. R. Recker[1], D. L. Kendler[2], S. Adami[3], C. Hughes*[4], E. Dumont*[5], R. C. Schimmer[4], C. Cooper[6]. [1]Creighton University, Omaha, NE, USA, [2]University of British Columbia, Vancouver, BC, Canada, [3]University of Verona, Verona, Italy, [4]F. Hoffmann-La Roche Ltd, Basel, Switzerland, [5]GlaxoSmithKline, Collegeville, PA, USA, [6]University of Southampton, Southampton, United Kingdom.

Bisphosphonate therapies are effective in normalizing the elevated rate of bone turnover associated with postmenopausal osteoporosis (PMO). Ibandronate (Boniva®) is a potent, nitrogen-containing bisphosphonate with proven antifracture efficacy when administered daily or intermittently in postmenopausal women with osteoporosis (3-year vertebral fracture risk reduction: 52% and 50%, respectively).[1] An ongoing, randomized, double-blind, phase III, non-inferiority study (MOBILE) is comparing the efficacy and safety of monthly oral 50/50mg (single doses on consecutive days), 100mg (single day) and 150mg (single day) ibandronate regimens with the proven oral daily (2.5mg) regimen in 1,609 women with PMO. In MOBILE, relative change (%) in the biochemical marker of bone resorption, sCTX, is a secondary efficacy endpoint, measured immediately prior to the scheduled ibandronate doses at 3, 6, 12 and 24 months. After 1 year, the magnitude of median sCTX suppression in the oral daily arm was 67.3% (Table). A comparable magnitude of sCTX suppression was reported in each of the monthly oral arms after 1 year (one month after dosing): 62.8%, 66.7% and 75.8% in the 50/50mg, 100mg and 150mg arms, respectively (Table). Substantial decreases in sCTX were also observed after 3 and 6 months (Table). At all assessment points, the 150mg regimen provided the greatest magnitude of sCTX suppression. In summary, monthly oral ibandronate rapidly suppresses bone resorption to normal levels within 3 months of initiation, and maintains this magnitude of suppression with continued therapy. Monthly oral ibandronate also provides a comparable magnitude of sCTX suppression to that observed with an oral daily ibandronate regimen of proven antifracture efficacy (3-year vertebral fracture risk reduction: 52%). These findings indicate that monthly oral ibandronate is a highly effective alternative to more frequently administered bisphosphonates in PMO.

1. Chesnut CH, et al. J Bone Miner Res (In press).

Table. Median relative change (%) from baseline in sCTX

	Daily ibandronate	Monthly ibandronate		
Month	2.5mg (n=318)	50/50mg (n=330)	100mg (n=315)	150mg (n=327)
3	-53.6	-50.0	-53.2	-66.1
6	-63.5	-60.7	-63.2	-73.4
12	-67.3	-62.8	-66.7	-75.8

Disclosures: R.R. Recker, F. Hoffmann-La Roche Ltd 2, S.

Monthly oral ibandronate significantly reduces bone resorption in postmenopausal osteoporosis: 1-year results from MOBILE

Reginster JY,[1] Kaufman JM,[2] Adami S,[3] Hughes C,[4] Pavelka T,[5] Saidenberg-Kermanac'h N,[6] Devogelaer JP[7]

[1]Centre Universitaire, Liège, Belgium; [2]University Hospital, Ghent, Belgium; [3]Chair of Rheumatology, University of Verona, Verona, Italy; [4]Roche Products Ltd, Welwyn Garden City, UK; [5]Roche s.r.o., Prague, Czech Republic; [6]Roche S.A., Boulogne-Billancourt, France; [7]Cliniques Universitaires St-Luc, Brussels, Belgium

SUMMARY

- Changes in biochemical markers of bone turnover with less frequent than weekly bisphosphonate dosing schedules are yet to be fully explored.
- Ibandronate (Bonviva™) is a potent, nitrogen-containing bisphosphonate with proven antifracture efficacy when administered as an oral medication, either continuously (daily) or intermittently with extended between-dose intervals (3-year vertebral fracture risk reduction: 52% and 50%, respectively).[1]
- In the MOBILE study, 50/50mg, 100mg and 150mg monthly oral ibandronate regimens were shown to be as effective (based on bone mineral density [BMD] endpoints) as the daily oral ibandronate regimen (2.5mg) in 1,609 women with postmenopausal osteoporosis.[2]
- Substantial and comparable decreases in the biochemical marker of bone resorption, serum CTX (sCTX), were also observed in the monthly and daily treatment arms after 1 year (secondary efficacy endpoint).
- Additional retrospective analyses revealed pronounced reductions in the biochemical marker of bone formation, bone alkaline phosphatase (BAP), which were within the ranges commonly associated with currently licensed oral bisphosphonates.
- These findings further demonstrate the comparable efficacy of monthly and daily oral ibandronate regimens in postmenopausal osteoporosis and offer further insights into the biomarker responses associated with less frequently administered bisphosphonates.

INTRODUCTION

- Continuously administered oral bisphosphonates (e.g. daily or weekly) are highly effective in normalizing the elevated rate of bone resorption commonly associated with postmenopausal osteoporosis.
- However, experience with less frequently administered bisphosphonates is less well documented.
- Ibandronate has proven antifracture efficacy when administered continuously (daily), and also when administered intermittently with extended dosing intervals.
- In the MOBILE study, 50/50mg, 100mg and 150mg monthly oral ibandronate regimens were shown to be as effective (based on BMD endpoints) as the daily oral ibandronate regimen (2.5mg; 3-year vertebral antifracture efficacy: 52%) in 1,609 postmenopausal women with osteoporosis.[2]
- Here, we describe the effect of monthly and daily oral ibandronate on the biochemical marker of bone resorption, sCTX (secondary efficacy endpoint).
- The findings of a recent post-hoc analysis of the biochemical marker of bone formation, BAP, are also described.

METHODS

Study design

- Multinational, randomized, double-blind, phase III, non-inferiority study.
- Postmenopausal women aged 55–80 years (years since menopause [YSM]: ≥5 years) with osteoporosis (lumbar spine [L2–L4] BMD T-score <–2.5 and ≥–5).
- Two-years' treatment with 50/50mg (single doses on consecutive days), 100mg (single day), 150mg (single day) monthly oral ibandronate or 2.5mg daily oral ibandronate.
- Study medication taken after an overnight fast of ≥6 hours and ≥1 hour before food, non-study medications and fluids other than water.
- Supplementation with daily oral calcium (500mg) and vitamin D (400IU).

Study endpoints

- Median change (%) from baseline in sCTX was a secondary efficacy endpoint (secondary efficacy endpoint).
- Median change (%) from baseline in BAP was analyzed retrospectively.
- sCTX and BAP concentrations were assessed in blood samples taken at baseline, 3, 6 and 12 months
  - all samples were taken immediately prior to the next scheduled dose of study medication and after an overnight fast of ≥6 hours.

Statistical analysis

- All efficacy parameters were evaluated in the per protocol (PP) analysis population
  - participants were excluded from the PP analysis in the event of: a biased BMD assessment, a baseline T-score >–2.5, an infringement of one of the study exclusion criteria, poor compliance or an unconfirmed menopausal status.
- Confirmatory intent-to-treat (ITT) analyses were also performed for all efficacy endpoints.

RESULTS

Patient characteristics

- A total of 1,609 women were randomized into the study.
- Of these, 1,290 women fulfilled the criteria for inclusion in the PP analysis (**Table 1**).

Table 1. **Patient demographics (mean; PP).**

	Dose			
	Daily (n=318)	50/50mg (n=330)	100mg (n=315)	150mg (n=327)
Age (years)	65	66	66	66
Weight (kg)	64	63	64	64
Height (cm)	157	157	158	158
Body mass index (kg/m²)	26	26	26	26
YSM (years)	18	18	18	18
History of previous fractures (%)	156 (49.4)	149 (45.2)	144 (45.7)	151 (46.2)
Lumbar spine (L2–L4) BMD (T-score)	–3.3	–3.3	–3.3	–3.3
Total hip BMD (T-score)	–1.8	–1.8	–1.8	–1.8
sCTX (ng/ml)*	0.485	0.520	0.510	0.500
BAP (ng/ml)*	10.545	11.080	11.445	11.520
25-OH-D (ng/ml)	25.6	24.4	25.2	24.7

*Median values

- The baseline characteristics of the PP analysis population were comparable across all study groups (**Table 1**).

sCTX

- Substantial and similar decreases in sCTX were observed in all treatment arms after 1 year (**Figure 1**).
- Pronounced decreases in sCTX were also observed by the first measurement, at 3 months (**Figure 1**).
- At all timepoints the 150mg monthly oral regimen provided the greatest magnitude of sCTX suppression.
- Comparable findings were obtained for the ITT population.

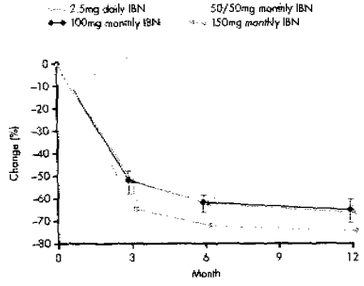


Figure 1. **Time course of median change (%) from baseline in sCTX with monthly and daily oral ibandronate (PP).**

BAP

- Pronounced and sustained decreases in BAP were also observed in all treatment arms (**Figure 2**).
- All measurements were within the ranges commonly observed with more frequently administered nitrogen-containing bisphosphonates.[3,4]

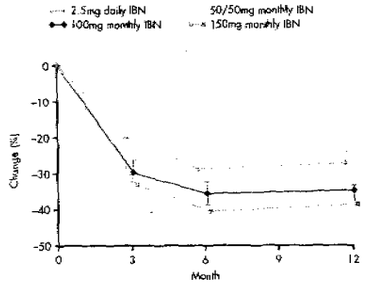


Figure 2. **Time course of median change (%) from baseline in BAP with monthly and daily oral ibandronate (PP).**

CONCLUSIONS

- Compared with a daily oral dosing schedule, monthly oral ibandronate regimens provide robust and similar suppression of sCTX and BAP in women with postmenopausal osteoporosis.
- All measurements of BAP were within the ranges commonly observed with current nitrogen-containing bisphosphonates.[3,4]
- These findings
  - further demonstrate the comparable efficacy of monthly and daily oral ibandronate regimens in postmenopausal osteoporosis
  - offer further insights into the biomarker response associated with less frequently than weekly administered oral ibandronate.

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US006143326A

United States Patent [19]

Möckel et al.

[11] Patent Number: 6,143,326

[45] Date of Patent: *Nov. 7, 2000

[54] **ORAL PHARMACEUTICAL PREPARATION CONTAINING IBANDRONAT**

[75] Inventors: **Jörn Möckel**, Heidelberg; **Rolf-Dieter Gabel**, Schwetzingen; **Heinrich Woog**, Laudenbach, all of Germany

[73] Assignee: **Roche Diagnostics GmbH**, Mannheim, Germany

[*] Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

[21] Appl. No.: **09/147,149**

[22] PCT Filed: **Apr. 21, 1997**

[86] PCT No.: **PCT/EP97/01940**

§ 371 Date: **Nov. 25, 1998**

§ 102(e) Date: **Nov. 25, 1998**

[87] PCT Pub. No.: **WO97/39755**

PCT Pub. Date: **Oct. 30, 1997**

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[51] **Int. Cl.**[7] **A61K 9/36**

[52] **U.S. Cl.** **424/482**; 424/480

[58] **Field of Search** 424/480, 482

[56] **References Cited**

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Primary Examiner—Thurman K. Page
Assistant Examiner—A. Berman
Attorney, Agent, or Firm—Arent Fox Kintner Plotkin Kahn

[57] **ABSTRACT**

The invention is directed to well-tolerated pharmaceutical compositions for oral application, containing ibandronate or a physiologically tolerable salt thereof as active substance, the administration form consisting of an active substance-containing inner portion enclosed in such fashion by a coat free of active substance that rapid release of the active substance takes place.

3 Claims, No Drawings

ORAL PHARMACEUTICAL PREPARATION CONTAINING IBANDRONAT

This is a 371 of PCT/EP97/01940 filed Apr. 21, 1997 which claims priority from German application DE19615812.5 filed Apr. 20, 1996.

The invention relates to pharmaceutical formulations of ibandronate or its physiologically tolerable salts for oral application, and to processes for producing same.

The active substance ibandronaic acid (1-hydroxy-3-(N-methyl-N-pentyl)aminopropyl-1,1-diphosphonic acid) and its salts (ibandronates), respectively, are among the class of diphosphonic acids which, in particular, are of interest in the treatment of bone diseases and particular disorders in the calcium metabolism such as hypercalcaemia, osteoporosis, tumor osteolysis or Paget's disease. In the treatment of the diseases mentioned, these active substances must be administered frequently and over a long period of time and therefore, the aim should be especially oral application in addition to intravenous application since it is the former which is more accepted by many patients.

Fundamentally, however, oral treatment is generally complicated by the well-known problems with oral tolerability of diphosphonic acids. Diphosphonic acids or their physiologically safe salts, and particularly aminodiphosphonic acids are known to give rise to irritations of the upper gastrointestinal tract (Fleisch H., Bisphosphonates in Bone Disease, Herbert Fleisch, Bern 1993, pp. 126–131). The same applies for diphosphonates which are also ingested at relatively low dosages of, e.g., less than 50 mg per single administration form. WO 93/09785 points out that the active substance risedronate ([1-Hydroxy-2-(3-pyridinyl) ethylidene]bisphosphonate), for example, may give rise to erosions and ulcerations in the upper sections of the digestive tract. Various references allude to the gastrointestinal intolerability of the active substances pamidronate (Dodwell D. et al., Biochemical Effects, Antitumor Activity and Pharmacokinetics of Oral and Intravenous Pamidronate (APD) in the Treatment of Skeletal Breast Cancer, Br. J. Cancer 62, 496 (1990)) and tiludronate (Reginster J. Y., Efficacy and Tolerability of a New Formulation of Oral Tiludronate (Tablet) in the Treatment of Paget's Disease of Bone, J. Bone Miner. Res. 9, 615–619 (1994)). In addition, it is also well-known that motility disorders may occur when swallowing the tablets and/or the tablets to be ingested get stuck due to the particular anatomic situation in the oesophagus. This may give rise to odynophagia or oesophageal strictures as well. Frequently, this is the case with elderly patients or with patients who, due to their disease, are forced to take the required tablets predominantly in a lying position.

Accordingly, in order to solve these problems, the art demanded that fundamentally, orally available administration forms be coated with a gastric juice-resistant film so that the active substance is released only subsequent to the passage through the stomach and thus, irritations of the stomach and the oesophagus would be avoided. For example, WO 95/08331 describes administration forms by which it is possible to reduce the irritating potential of alendronate and other diphosphonates in oral application.

Due to the above-described oral intolerability of diphosphonates, there has been a search for more tolerable administration forms for a number of these active substances. In particular, oral administration forms coated with gastric juice-resistant coatings have been developed in this context. Such coatings are the choice in protecting the upper sections of the gastrointestinal tract, particularly the oesophagus or the stomach, from intolerable active substances. These gastric juice-resistant coatings on solid oral administration forms dissolve only at higher pH values of about 5.5 on, so that in the acidic gastric medium, being at a pH value far below 5.5, no active substance will be released from the administration form and thus, the stomach is protected from irritations caused by the active substance. As no active substance is released in the stomach, it is possible at the same time to prevent oesophagitis or other irritations of the oesophagus caused by the refluxing gastric contents containing active substance. As a consequence, DE 59 005 517 (EP 421,921) describes a gastric juice-resistant oral administration form for pamidronate which is suitable in reducing the risk of gastric ulcerations. Furthermore, WO 93/09785 illustrates such an administration form for risedronate, WO 95/08331 for alendronate and other diphosphonates.

The potential advantages of the gastric juice-resistant administration forms are contrasted by a number of drawbacks. Thus, resorption with these administration forms may be reduced as compared to forms releasing in a pH-independently rapid fashion, or resorption is substantially more variable as compared to conventional forms, thus impairing or jeopardizing therapeutical safety. Therefore, there is a demand in alternative administration forms for these active substances in order to avoid the disadvantages of the gastric juice-resistant forms and nevertheless, be capable of providing sufficient protection from these aminobisphosphonates having aggressive effects on the gastric mucosa.

Surprisingly, it was found that improved oral tolerability in the case of the ibandronate active substance is already achieved when peroral administration forms are coated with an adjuvant coating or film in such fashion that the active substance is dissolved within a short period of time and correspondingly high local concentrations of active substance are achieved in the stomach. The film dissolving upon contact with digestive juice is preferably a coating which dissolves pH-independently. The adjuvant coating may be coated using methods common in pharmaceutical technology. Although this coating does not prevent dissolution of ibandronate in the stomach, it was surprising that no significant side effects were observed in clinical studies using ibandronate even at high dosages. Despite the fact that the administration forms are coated with a film which quickly releases the active substance, there are no irritations in the oesophagus when swallowing the tablets, and oesophagitis does not occur. This is particularly advantageous since the administration forms of the invention are also well-tolerated by patients lying in bed.

According to the invention, solid oral formulations of ibandronate are provided, consisting of a core containing the active substance, which is coated with an adjuvant coating free of active substance, which either dissolves independently of the pH value or is removed from the solid oral formulation upon contact with digestive juice. In this way, relatively rapid disintegration of the drug form and release of the active substance within a short period of time are ensured, whereby high local concentrations of the active substance are achieved. The coating may be applied using methods such as film coating, press coating, tablet coating, encapsulating or micro-encapsulating. The release of active substance from the appropriately coated solid administration forms for oral application, such as film tablets, coated tablets, laminated tablets, capsules, or microcapsules, takes place more rapidly as compared to the gastric juice-resistant administration forms. According to the invention, at least 30% of the contained ibandronate dose, but preferably at

least 75% and, in particular, at least about 85% is released rapidly and independently of the pH value within the physiological pH range. Preferably, the time period required to achieve these release percentages is less than 2 hours, more preferably less than 1 hour, with about 1–30 minutes being particularly preferred. It is particularly preferred that the release is about 80–90% within a time period of up to 15 minutes. Conveniently, the release of active substance is estimated within the scope of an in vitro experiment according to well-known standardized procedures.

Surprisingly, rapid release of the active substance does not result in the undesirable side effects usually known for diphosphonic acids as described above, despite the high local concentrations of active substance (i.e., despite the high gradient of active substance) thereby generated in the stomach. Rather, it was found that despite the rapid release of active substance, the problem of occurring gastrointestinal disorders is avoided, quite surprisingly. Furthermore, it has been observed that among patients treated with such rapidly releasing administration forms of ibandronate, there were significantly less cases of nausea, vomiting, pain or diarrhoea than otherwise observed when administering aminobisphosphonates.

The coatings with rapid release of active substance in the meaning of the invention can be applied to all the suitable peroral administration forms such as tablets, capsules, coated tablets, pellets, granulates or powders. These administration forms consist of mixtures of active substances with pharmaceutical adjuvants or of pure active substances. Coating may be performed using various methods common in pharmacy. For example, suitable methods use tablet coating units, film coating units, tablet presses for press coating, encapsulating machines, or micro-encapsulating units, such as facilities for spray freezing and spray embedding, facilities for producing simple or complex coacervates.

In the meaning of the invention, pharmaceutically common or physiologically safe polymers are possible as film-forming agents. Film-forming agents in the meaning of the invention are derived from, e.g., the groups of cellulose derivatives, dextrins, starches and starch derivatives, polymers based on other carbohydrates and derivatives thereof, natural gums such as gum arabic, xanthans, alginates; polyacrylic acid, polyvinyl alcohol, polyvinyl acetate, polyvinylpyrrolidone, polymethacrylates and derivatives thereof (Eudragit®), chitosan and derivatives thereof, shellac and derivatives thereof. In addition to these film-forming agents, substances from the class of wax and fat substances may be used to produce the coatings according to the invention.

Preferably, the soluble alkyl- or hydroxyalkylcellulose derivatives such as methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, methylhydroxyethylcellulose, methylhydroxypropylcellulose, or sodium carboxymethylcellulose are possible as cellulose derivatives. In a preferred variant of an embodiment of the invention, methylhydroxypropylcellulose is employed. The usual cellulose derivatives suitable for pharmaceutical purposes, with varying degrees of substitution and/or varying molecular weights corresponding to varying viscosity levels of the aqueous solutions, may be used as suitable film-forming agents on the basis of cellulose. Likewise, insoluble cellulose derivatives such as ethylcellulose may be employed.

In the case of polymethacrylates, cationic copolymerizates of dimethylaminoethyl methacrylate with neutral methacrylic esters (Eudragit® E), copolymerizates of acrylic and methacrylic esters having a low content of quaternary ammonium groups (described in "Ammonio Methacrylate Copolymer Type A or Type B" USP/NF, Eudragit® RL and RS, respectively), and copolymerizates of ethyl acrylate and methyl methacrylate with neutral character (in the form of an aqueous dispersion, described in "Polyacrylate Dispersion 30 Per Cent" Ph. Eur., Eudragit® NE 30 D) are possible.

Similarly, the use of film-forming agents usually employed in the production of gastric juice-resistant films is possible as long as pH-independently rapid release of the active substance from the appropriately coated administration form, as described above, is ensured, e.g., by a thin layer thickness of the coating or other measures such as an extremely high percentage of pore-forming agents or the like. Anionic copolymerizates of methacrylic acid and methyl methacrylate (described in "Methacrylic Acid Copolymer, Type C" USP/NF, Eudragit® L and S, respectively, or in the form of the Eudragit® L 30 D aqueous dispersion), acidic cellulose derivatives such as cellulose acetate phthalate, cellulose acetate trimellitate and methylhydroxypropylcellulose phthalate, polyvinyl acetate phthalate, etc. may be used as such films.

In principle, all the film-forming agents may be employed alone as well as in mixtures of two or more filmforming agents.

If required, the films may contain additional adjuvants such as plasticizers, pore-forming agents, filling agents, colorants, pigments, antifoam agents, antistick agents, and the like.

According to the invention, polymers and adjuvants possibly required in addition, as were described in the preceding paragraph, are possible for press coating as far as they can be processed by means of press coating technology. In addition, all the pharmaceutically common or physiologically tolerable adjuvants which are suited to form a closed coat by press coating on the drug forms to be covered may be used in the meaning of the invention. In particular, these include adjuvants as are common in conventional tabletting, specifically filling agents from the group of carbohydrates such as lactose, saccharose, glucose and other sugars, microcrystalline cellulose, starches and starch derivatives, sugar alcohols such as mannitol, sorbitol, xylitol, inorganic filling agents such as phosphates and carbonates. According to the invention, other adjuvants as required in the production of conventional tablets, such as binding agents, disintegrants, flow agents, release agents, taste improvers, pigments, and coloring agents may be contained in addition to the filling agents.

According to the invention, all the adjuvants described above may be employed for tablet coating, in principle. In addition, special adjuvants for tablet coating may be employed according to the invention, such as palatinite, bentonite, calcium sulfate as filling agents, polyethylene glycol or polyethylene glycol fatty acid esters as release agents, colloid silicic acid as drying agent and structuring agent, magnesium oxide as spreading powder, pharmaceutically common or physiologically safe fats and waxes as glossing agents.

In the meaning of the invention, all the pharmaceutically common capsules such as gelatin hard capsules, soft gelatin capsules, starch capsules are possible as capsules. The capsules may be filled with powders, granulates, pellets or tablets. In general, all the pharmaceutically common solid, liquid and semi-solid formulations may be filled into the capsules of the invention.

For micro-encapsulating the active substance or formulations of the active substance, all the polymeric film-

forming agents mentioned above may be used according to the invention. Here, the polymers may be used alone as well as in mixtures of multiple polymers, and also together with other adjuvants, if necessary.

In the following, the invention will be illustrated by way of embodiments which are not intended as limitation.

For example, The ibandronate active substance is employed in amounts of 0.1–100 mg per single dosage unit. Preferably, the dosage is at least ca. 1 mg, 5 mg, 10 mg, or 20 mg as lower limit for the amount of active substance in a single administration form. The upper limit is about 250 mg, particularly 100 mg and 50 mg, respectively.

EXAMPLE 1

Ibandronate-containing core: Ibandronate dose [mg] in 200 mg tablet core:	10.0	20.0	50.0
Ibandronate-free coat [mg]:			
Methylhydroxypropylcellulose	5.1425	5.1425	5.1425
Titanium dioxide	2.4650	2.4650	2.4650
Macrogol	1.5000	1.5000	1.5000
Talc	0.8925	0.8925	0.8925
Total film coated	10.0000	10.0000	10.0000

Film-coating is carried out in common apparatus. Coating conditions: tablet charge 140 kg; feed air temperature: 60° C.

EXAMPLE 2

Ibandronate-containing core: Ibandronate dose in 100 mg tablet core [mg]:	0.1	2.5	5.0
Ibandronate-free coat [mg]:			
Methylhydroxypropylcellulose	2.057	2.057	2.057
Titanium dioxide	0.986	0.986	0.986
Macrogol	0.600	0.600	0.600
Talc	0.357	0.357	0.357
Total film coated	4.000	4.000	4.000

Film-coating in a conventional 250 l tablet coating tank. Coating conditions: tablet charge 144 kg.

EXAMPLE 3

Ibandronate-containing core: Ibandronate dose [mg] in 200 mg tablet core:	10.0	20.0	50.0
Ibandronate-free coat [mg]:			
Talc	2.00	2.00	2.00
Lactose	1.40	1.40	1.40
Methylhydroxypropylcellulose	0.80	0.80	0.80
Titanium dioxide	0.80	0.80	0.80
Macrogol	0.40	0.40	0.40
Ethyl methyl methacrylate copolymer*	0.04	0.04	0.04
Polysorbate	0.04	0.04	0.04
Total film coated	5.48	5.48	5.48

*Employed in the form of Eudragit ™ NE 30 D as an aqueous dispersion.

Film-coating in a conventional 15 l tablet coating tank. Coating conditions: tablet charge 13.0 kg.

EXAMPLE 4

Ibandronate-containing core: Ibandronate dose [mg] in 86 mg tablet core:	10
Ibandronate-free coat [mg]:	
Saccharose	37.844
White clay	8.138
Talc	1.000
Macrogol	2.848
Glucose syrup	2.035
Titanium dioxide	1.628
Polyvidone	0.407
Montan glycol wax	0.100
Total tablet coating applied	54.000

Tablet coating in a conventional 15 l tablet coating tank with dip pipe.

EXAMPLE 7

Ibandronate in laminated tablet	
Ibandronate-containing core:	
Final weight:	86 mg
Format of core:	7 mm in diameter, plane, with facettes
Ibandronate dose in tablet core:	10 mg
Ibandronate-free coat:	
Lactose	270 mg
Microcrystalline cellulose:	90 mg
Pressing tool:	12 mm in diameter
Final weight of laminated tablet:	446 mg

Pressing by means of a hand press using conventional procedures.

What is claimed is:

1. A method of treating a bone disease in a patient in need thereof, comprising orally administering to the patient a pharmaceutical formulation comprising a tablet core containing about 0.1 to 100 mg of ibandronate and a coating which is free of ibandronate and has the following proportional composition:

(a) about 51.425% by weight of methylhydroxypropylcellulose;

(b) about 24.650% by weight of titanium dioxide;

(c) about 15.000% by weight of polyethylene glycol; and

(d) about 8.925% by weight of talc.

2. The method of claim 1, wherein the bone disease is related to a disorder in calcium metabolism.

3. The method of claim 1, wherein the bone disease is selected from the group consisting of hypercalcemia, osteoporosis, tumor osteolysis, and Paget's disease.

* * * * *

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A1

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(54) Title: PROCESS FOR THE PREPARATION OF ORAL PHARMACEUTICAL COMPOSITIONS COMPRISING BIPHOSPHONATES

(57) Abstract

The invention relates to a process for the preparation of bisphonate–containing pharmaceutical compositions for oral application, wherein the active substance is wet–granulated in manner known per se in a fluidised–bed granulator using adjuvants which have no abrasive action and wherein the wet granulate is then dried in the fluidised bed, screened through a screen having a suitable mesh width and further processed by techniques known per se to form pharmaceutical compositions.

The invention is preferably used for producing pharmaceutical preparations which contain the active substance in a proportion of up to 50 mg per unit dose, preferably up to 10 mg, particularly preferably 0.1 to 5 mg and 0.1 to 2.5 mg. Ibandronate is a particularly preferred active substance, particularly in the form of Na-Ibandronate monohydrate.

The adjuvants which do not have an abrasive effect during granulation may, according to the invention, be fillers such as lactose in hydrate or anhydrate form, sugar alcohols such as mannitol; tableting adjuvants such as cellulose in microcrystalline or fibrous form; and binders such as polyvinyl pyrrolidone (Povidone USP) or cellulose ethers such as methyl hydroxypropyl cellulose. At least one adjuvant is used which acts as binder.

Preferably at least one of the adjuvants is lactose, microcrystalline cellulose or polyvinyl pyrrolidone. In a preferred embodiment 1-99% by weight lactose, 1-99% by weight microcrystalline cellulose, 0.1-20% by weight are used, particularly preferably 25-75% by weight lactose, 10-20% by weight microcrystalline cellulose, and 2-3% by weight polyvinyl pyrrolidone.

The granulate is further processed by known methods, using additional adjuvants if required, into tablets, chewing tablets, effervescent tablets, film tablets, dragees and pellets or filled into hard gelatine capsules or sachets. The adjuvants used in further processing are conventional lubricants, e.g., stearic acid, disintegrants, e.g., cross-linked polyvinyl pyrrolidone (Crospovidone USPNF), flow-regulators,

in-process control: 220.05 mg
Content of active substance found in the capsules produced in this way: 94.9% ± 1.9%
(n = 10 individual measurements)

Example 3:

Production of ibandronate 1.0 mg tablets after granulation in a fluidised bed (batch size for 60.000 tablets).

Constituents		g
Na-Ibandronate	64.14	
Lactose		4405.86
Polyvinyl pyrrolidone		150.00
Polyvinyl pyrrolidone, cross-linked (disintegrant)		300.00
Stearic acid (lubricant)		120.00
Microcrystalline cellulose		900.00
Colloidal SiO_2 (flow agent)		60.0

The amount of active substance per tablet is equivalent to 1.0 mg of free acid.

Lactose and 600 g microcrystalline cellulose were granulated with an aqueous solution of polyvinyl pyrrolidone and ibandronate in a fluidised-bed granulator (Aeromatic type). The wet granulate was dried in the fluidised bed (Aeromatic type), passed through a 1.0 mm screen, mixed with disintegrant, lubricant, flow-regulator and 300 g microcrystalline cellulose (Turbula-type mixer, mixing time 5 minutes)

and converted into tablets in a tableting press (Korsch type) having a capacity of 25,000 tablets per hour.

Set weight of tablets:	100.0 mg
Actual weight of tablets according to in-process control:	101.3 mg

Content of active substance found per tablet produced in this way: 98.3% ± 4.2% (n = 10 individual measurements).

The active substance content of the tablets was within the acceptance limits.

Example 4

Production of ibandronate 0.1 mg tablets after granulation in a fluidised bed (batch size for 150.000 tablets).

Constituents	g
Na-Ibandronate monohydrate	16.95
Lactose	11158.05
Polyvinyl pyrrolidone	375.00
Polyvinyl pyrrolidone, cross-linked (disintegrant)	750.00
Stearic acid (lubricant)	300.00
Microcrystalline cellulose	2250.00
Colloidal SiO_2 (flow agent)	150.00

The amount of active substance per tablet is equivalent to 0.1 mg of free acid.

Lactose and 1500 g microcrystalline cellulose were granulated with an aqueous solution of polyvinyl

pyrrolidone and ibandronate in a fluidised-bed granulator (Aeromatic type). The wet granulate was dried in the fluidised bed (Aeromatic type), passed through a 1.0 mm screen, mixed with disintegrant, lubricant, flow-regulator and 750 g microcrystalline cellulose (Turbula-type mixer, mixing time 10 minutes) and converted into tablets in a tableting press (Korsch type) having a capacity of 60,000 tablets per hour.

Set weight of tablets:	100.0 mg
Actual weight of tablets according to in-process control:	101.3 mg

Content of active substance found per tablet produced in this way : 98.5% ± 2.4% (n = 10 individual measurements).

The active substance content of the tablets was within the acceptance limits.

C L A I M S

1. A process for the preparation of pharmaceutical compositions for the oral application of bisphosphonates, wherein the bisphosphonate is wet-granulated in manner known per se in a fluidised-bed granulator using adjuvants which have no abrasive action and wherein the wet granulate is then dried in the fluidised bed, screened through a screen having a suitable mesh width and further processed by techniques known per se to form pharmaceutical compositions.

2. A process according to claim 1, wherein the bisphosphonate in solution or suspension and together with an aqueous binder is sprayed on to other adjuvants and granulated.

3. A process according to claim 1, wherein the bisphosphonate and the adjuvants in dry powder form are placed in a fluidised-bed reactor and granulated by the spraying of water into the powder mixture, which in that case contains a binder, or the powder containing the active substance is granulated by the spraying in of an aqueous binder solution.

4. A process according to any of claims 1 to 3, wherein the bisphosphonate used is alendronate, clodronate, EB-1053, etidronate, ibandronate, incadronate, neridronate, olpadronate, pamidronate, risedronate, tiludronate, YH 529 or zoledronate in the form of the free acid or a pharmaceutically compatible salt or hydrate, particularly the sodium salt.

5. A process according to claim 4, wherein the bisphosphonate used is ibandronate.

6. A process according to any of claims 1 to 5, wherein at least one of the adjuvants is: lactose, microcrystalline cellulose or polyvinyl pyrrolidone.

7. A process according to claim 6, wherein the adjuvants used are 1-99% by weight lactose, 1-99% by weight microcrystalline cellulose and 0.1-20% polyvinyl pyrrolidone.

8. A process according to claim 7, wherein 25-75% by weight lactose, 10-20% by weight microcrystalline cellulose and 2-3% by weight polyvinyl pyrrolidone are used.

9. A process according to any of claims 1 to 8, wherein further processing into tablets, capsules, film tablets, dragees, pellets, effervescent tablets, chewing tablets or granulates in sachets is carried out.

10. A process according to claim 9, wherein further processing is effected with the addition of 0.05 - 3% by weight stearic acid to the mixture.

11. A process according to any of claims 1 to 10 for the preparation of forms of administration containing up to 50 mg active substance per unit dose.

12. Pharmaceutical compositions for the oral application of bisphosphonates when made according to any one of claims 1 to 11.

e.g., colloidal silicon dioxide, tableting adjuvants etc. In one preferred embodiment the further processing of the granulate is carried out with the addition of stearic acid as lubricant in quantities of less than 5% by weight referred to the total weight of the form of administration, particularly 0.05 to 3% by weight of stearic acid.

Preparation of pharmaceutical compositions according to the invention by fluidised-bed granulation, particularly by the drying process in the fluidised-bed granulator, results in less intensive contact between the material and the surface of the apparatus, thus surprisingly reducing the loss of active substance. This is particularly advantageous when the active substance content of the unit dose is small. This substantially avoids the above-described disadvantages in the conventional production of forms for oral administration.

The invention will now be explained in further detail with reference to examples, without being limited thereto.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado
ALICIA LLOREDA RICAURTE
Apoderado

ASUNTO	Radicación	04-096462
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	10374
	Folios	18

Patente de Invención ☒ Patente de Modelo de Utilidad ☐

Vía Nacional ☐

Vía PCT (fase nacional) ☒ Cap.I ☐ Cap. II ☒

No. Sol. Internacional PCT/EP03/04629
Fecha de Presentación Internal. 02 de Mayo de 2003

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

1.1.	Descripción:	Folios: 61 a 103 como se radicó inicialmente
1.2.	Reivindicaciones:	Folios 18 a 20 como se radicó inicialmente
		Folios 51 a 52 modificadas en fase nacional
		Folios 109 a 110 modificadas en fase nacional
1.3.	Prioridad:	Folios: 1
		10 de Mayo de 2002, EP, 02010136.6

1.4. Respuesta del solicitante: Folios: 93 a 123

2. Análisis de la Prioridad

- La fecha de prioridad del 10 de Mayo de 2002 y su correspondiente documento, corresponden con la materia solicitada de protección.

3. Objeto de la invención

- Título de la solicitud: **"ÁCIDO BIFOSFÓNICO PARA EL TRATAMIENTO Y PREVENCIÓN DE OSTEOPOROSIS"** Folio 1.

El objeto de la presente solicitud de patente de invención consiste en el empleo de los ácidos bifosfónicos o las sales farmacéuticamente aceptables de los mismos, especialmente el ácido ibandrónico para la prevención y tratamiento de la osteoporosis.

Reivindicación 1-6: Medicamento

El problema planteado en esta solicitud es la prevención o tratamiento de trastornos caracterizados por un aumento patológico de la resorción ósea.

Para solucionar este problema técnico la solicitud en estudio proporciona un medicamento de un ácido bifosfónicos o las sales farmacéuticamente aceptables de los mismos.

- **Clasificación Internacional de Patentes (IPC):** *A61K9/36; A61K9/20; A61K9/28; A61K31/662; A61K31/663; A61K47/04; A61K47/12; A61K47/26; A61K47/32; A61K47/34; A61K47/38; A61K9/30; A61K9/20; A61K47/02.*

4. De la solicitud de Patente

4.1. Descripción *(artículo 28 D. 486)*

- No se encontraron datos comparativos con las composiciones previamente divulgadas que presenten el efecto técnico inesperado alcanzado y sus ventajas superiores.
- No se encuentran sustentados ejemplos de las formulaciones del medicamento con 100 o 150mg de principio activo.

4.2. Reivindicaciones *(artículo 30 D 486)*

- La reivindicación 1 se encuentra enunciada por "administrado mensualmente" lo cual se refiere a un método de tratamiento.
- La reivindicación 6 se refiere al medicamento de forma general y amplia sin encontrarse plenamente caracterizado, sin encontrarse acorde con lo descrito en el ejemplo 1. (Ver folio 50)

5. Determinación del Estado de la Técnica

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es: 13/11/2000 se encontraron los siguientes documentos del estado de la técnica relacionados, que pueden afectar la patentabilidad del objeto de la presente solicitud:

N°	Documento	Título	Fecha de publicación
D1	US 6,143,326	"Oral pharmaceutical preparation containing ibandronat"	30/10/1997
D2	WO 00/21541	"Process for the preparation of oral pharmaceutical compositions comprising biphosphonates"	20/04/2000

6. Análisis de patentabilidad (artículo 14 D486)

6.1 Novedad (artículo 16 D486)

6.1.1. Solicitud presentada

La reivindicación 1 de la solicitud presentada se refiere a un **medicamento oral** caracterizado porque comprende **100mg** o **150mg** de un **ácido bifosfónico** o una sal farmacéuticamente aceptable del mismo y uno o más excipientes farmacéuticamente aceptables.
La reivindicación 2 se refiere al **ácido bifosfónico** como **ácido ibandrónico** o **una sal farmacéuticamente aceptable.**

D1 divulga preparaciones farmacéuticas orales que contienen **ibandronato o una sal tolerable fisiológicamente** como sustancia activa conteniendo una porción interior rodeada por una cubierta libre de sustancia activa de rápida liberación (Ver resumen)

La reivindicación 1 de **D1** se refiere a una formulación que comprende un núcleo de tableta que contiene entre 0.1 a 100mg de ibandronato y una cubierta la cual es libre de ibandronato (Ver columna 6, líneas 46-56)

D1 también se refiere a la cantidad de la sustancia activa de ibandroanto es empleada en cantidades de 0.1-100mg por unidad de dosificación única, **siendo el límite superior cerca de 250mg**, particularmente 100mg y 50mg respectivamente. (Ver columna 5, líneas 7-12)

Conforme a lo anteriormente descrito se concluye que **el medicamento oral** caracterizado porque comprende **100mg o 150mg** de un **ácido bifosfónico** o una sal farmacéuticamente aceptable del mismo y uno o más excipientes farmacéuticamente aceptables donde el **ácido bifosfónico** es **ácido ibandrónico** o **una sal farmacéuticamente aceptable** del mismo, en comprimidos recubiertos, no son novedosos.

6.1.2. Solicitud presentada

La reivindicación 5 se refiere a un medicamento que comprende un ácido bifosfónico o una sal farmacéuticamente aceptable del mismo, donde es la **sal monósódica de ácido ibandrónico, monohidrato**

La reivindicación 6 se refiere al medicamento, caracterizado porque es un **comprimido recubierto por una película**, donde **los excipientes son** seleccionados entre el grupo conformado por:

- Lactosa, polivinilpirrolidona, celulosa microcristalina, crospovidona, ácido esteárico y dióxido de silicio y
- Hidroxipropilmetilcelulosa, óxido de titanio, talco y polietilénglicol 6000

Anterioridades

D1 es el estado más cercano de la técnica pues divulga una formulación que comprende un núcleo de tableta que contiene entre **0.1 a 100mg de ibandronato** y una cubierta la cual es libre de ibandronato con la siguiente proporción: (Ver columna 6, líneas 46-56)

- **51.425%** por peso de **hidroxipropilmetilcelulosa**
- **24.650%** por peso de **dióxido de titanio**
- **15.000%** por peso de **polietilénglicol**
- **8.925%** por peso de **talco**

El ejemplo de la solicitud presentada utiliza en las tabletas de 50mg de ibandronato los mismos excipientes enunciados en **D1**, por lo tanto no se consideran novedosos

los comprimidos recubiertos donde se utilizan como excipientes: hidroxipropilmetilcelulosa, óxido de titanio, talco y polietilénglicol. (Ver folio 50):

D2 divulga previamente un proceso para la preparación de composiciones farmacéuticas orales que comprenden bifosfonatos. (Ver resumen)

El ibandronato es la sustancia activa preferida en **D2** particularmente en la forma de **monohidrato de ibandronato sódico** en una proporción hasta **50mg.** (Ver página 6, líneas 1-7)

El ejemplo 3 y 4 de **D2**, enseñan formulaciones para tabletas las cuales contienen **lactosa, polivinilpirrolidona, celulosa microcristalina, crospovidona, ácido esteárico y dióxido de silicio** (Ver página 10 y 11).

La reivindicación 7 enseña que los adyuvantes usados se encuentran en las proporciones de **lactosa en 1-99%** por peso, **polivinilpirrolidona en 0.1-20%** por peso, **celulosa microcristalina en 1-99%** por peso. (Ver página 14, líneas 8-11-**D2**)

La reivindicación 9 enseña que el proceso aplica a **tabletas recubiertas**. (Ver página 14, líneas 19-20-**D2**)

La reivindicación 10 se refiere al peso de **ácido esteárico** a la mezcla en una proporción de **0.05-3%** (Ver página 14, líneas 24-26-**D2**)

El solicitante en el ejemplo enseña los mismos componentes previamente divulgados para el núcleo de las tabletas tales como **lactosa** en 1-99% por peso, **polivinilpirrolidona** en 0.1-20% por peso, **celulosa microcristalina** en 1-99% por peso, crospovidona y dióxido de silicio (Ver folio 50), careciendo por lo tanto de novedad el uso de los excipientes anteriormente enunciados.

6.2 Nivel inventivo *(artículo18 D486)*

Es evidente para el experto en la materia que de acuerdo a lo previamente divulgado en **D1** y **D2,** se obtendría **el medicamento oral de ibandronato monosódico monohidrato en comprimidos recubiertos** de **100mg o 150mg,** utilizando los mismos excipientes antes enseñados tales como lactosa, polivinilpirrolidona, celulosa microcristalina, crospovidona, ácido esteárico y dióxido de silicio e hidroxipropilmetilcelulosa, óxido de titanio, talco y polietilénglicol.

El problema técnico planteado en esta solicitud como es obtener **"es la prevención o tratamiento de trastornos caracterizados por un aumento patológico de la resorción ósea",** sería solucionado fácilmente por el experto en la materia con base en las composiciones farmacéuticas divulgadas en **D1** y **D2**, de manera que este lo lograría fácil y obviamente sin necesidad de emplear Habilidad Inventiva.

Por lo tanto las reivindicaciones 4 a 6 carecen de nivel inventivo.

6. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

N°	Documento N°	Reivindicaciones afectadas	Requisito que afecta
D1	US 6,143,326	1-3	Novedad

			Nivel Inventivo
D2	**WO 00/21541**	**1-3**	**Novedad** **Nivel Inventivo**

7. Respuesta a los argumentos del solicitante:

- Los documentos anexados por el solicitante según folios 111 a 123 no evidencian, el empleo del medicamento del solicitante según las reivindicaciones 1 a 6.
  Los documentos se refieren al empleo de las dosis de 100mg o 150mg para su correspondiente administración única mensual como método de tratamiento, lo cual no es patentable de acuerdo a la legislación vigente colombiana. La cantidad de fármaco tal como 100mg o 150mg no es elemento característico único que define el medicamento en su conjunto y que permite una única administración mensual.
- De acuerdo con las observaciones del solicitante con respecto a la documentación allegada por Tecnoquímicas corresponde a **"remisión de información"**

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de 60 días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha _____

CONCEPTO TÉCNICO No. 01619	**EXAMINADOR TÉCNICO** Código No. 202070

14

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
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Folio 20041107 16:20:06 Dep 2020 NUEVAS CREACIONES
No. 11 PATENTES Exp 379 FASE NACIONAL
No 444 10-SEP-08 STAREQUE Folios 50

Señor
SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E. S. D.

Re: P1.- **F. HOFFMANN-LA ROCHE AG** -Solicitud de Patente de Invención en Fase Nacional PCT para "**ÁCIDO BISFOSFÓNICO PARA EL TRATAMIENTO Y PREVENCIÓN DE OSTEOPOROSIS**".-Clase **A61P 19/10**.-Expediente número **04-096.462.-**

1. Me refiero al auto dictado por ese Despacho notificado por fijación en lista el 15 de Agosto de 2008.

2. Con el fin de responder a las objeciones expuestas por el señor Examinador en su Concepto Técnico No. **1619** bajo los acápites de Claridad, Novedad y Nivel inventivo, atentamente me permito presentar los siguientes argumentos técnicos y las siguientes modificaciones hechas en el capítulo reivindicatorio de la solicitud en cuestión, mediante lo cual no sólo se superan dichas objeciones, sino que además se demuestra en forma contundente la patentabilidad de la presente invención.

3. **MODIFICACIONES A LA SOLICITUD**

Inicialmente me permito manifestar que el solicitante ha decidido alterar el capítulo reivindicatorio actualmente presentado, **modificando** la reivindicación 1 y **eliminando** la reivindicación 6. Por lo tanto, el nuevo capítulo reivindicatorio que se remite junto con el presente memorial está compuesto por cinco (5) reivindicaciones cuyo sustento se analiza a continuación:

- La nueva reivindicación 1 está dirigida a proteger un medicamento para administración oral caracterizado porque es un comprimido recubierto por una película, en donde el núcleo del comprimido comprende:

  - 100 mg o 150 mg de un ácido bisfosfónico o una sal farmcéuticamente aceptable del mismo; y

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- uno o mas excipientes farmacéuticamente aceptables seleccionados del grupo conformado por: lactosa, polivinilpirrolidona, celulosa microcristalina, crospovidona, ácido esteárico y dióxido de silicio;

y en donde el recubrimiento del comprimido comprende uno o mas excipientes farmacéuticamente aceptables seleccionados entre el grupo conformado por: hidroxipropil metilcelulosa, dióxido de titanio, talco y polietilenglicol 6000.

Dicha nueva reivindicación 1 presenta adecuado sustento, por ejemplo, en la página 14 (líneas 2 a 24) de la descripción.

Ahora bien, en este punto resulta de gran importancia mencionar que en la página 8 (línea 15) del texto correspondiente a la publicación internacional de la presente solicitud (documento WO 03/095029), así como en la página 14 (líneas 20 y 21) de la descripción presentada en fase nacional, se hace referencia a la composición del núcleo del comprimido, hecho que constituye un evidente error involuntario debido a que el núcleo del comprimido no está compuesto por uno o más excipientes farmacéuticamente aceptables seleccionados entre hidroxipropil metilcelulosa, dióxido de titanio, talco y polietilenglicol 6000, sino que está compuesto por uno o más excipientes farmacéuticamente aceptables seleccionados entre lactosa, polivinilpirrolidona, celulosa microcristalina, crospovidona, ácido esteárico y dióxido de silicio, tal como se encuentra definido en las líneas 11 a 15 de la página 8 y en la Tabla 1 (página 10) del documento WO 03/095029.

En este sentido, dicho error ha sido corregido dentro del texto de la descripción presentada en fase nacional, mediante el reemplazo del término "núcleo" por el término correcto "recubrimiento" en la página 14 (línea 20) de dicho documento (anexo iii).

- Por su parte, las reivindicaciones 2 a 5 actualmente presentadas no han sido modificadas.

En vista de lo anterior, me permito resaltar que las modificaciones realizadas al capítulo reivindicatorio de la presente solicitud **no amplían de manera alguna el alcance establecido en la memoria descriptiva originalmente presentada**, cumpliendo a cabalidad con los requisitos de patentabilidad estipulados en el Artículo 34 de la Decisión 486 de 2000.

4. CLARIDAD DE LA SOLICITUD

El señor Examinador ha objetado la claridad de la presente solicitud con base en los siguientes argumentos:

Descripción

- ***"No se encontraron datos comparativos con las composiciones previamente divulgadas que demuestren su aporte al estado de la técnica, y el efecto inesperado alcanzado"***

Frente a este particular, inicialmente me permito mencionar que el señor Examinador argumenta en su Concepto Técnico que los documentos remitidos a ese Despacho junto con la respuesta dada al Artículo 45 notificado el 14 de marzo de 2008 y respondido el 13 de junio de 2008, *"no evidencian el empleo del medicamento del solicitante según las reivindicaciones 1 a 6".*

En vista de lo anterior, me permito presentar ante ese Despacho un compendio actualmente publicado en internet *(www.emc.medicines.org.uk)* de las principales características fisicoquímicas y farmacológicas del medicamento revelado en la presente solicitud, es decir, del comprimido recubierto con una película que comprende 150 mg de ácido ibandrónico (ANEXO IV). En dicho documento se describe no solamente la composición cualitativa y cuantitativa de dicho medicamento *(composición que efectivamente corresponde a lo definido en la nueva reivindicación 1 de la invención en cuestión),* sino que también se revela un resumen de los principales resultados experimentales obtenidos por el solicitante en relación con la actividad farmacológica del medicamento, los cuales, por ejemplo, demuestran inequívocamente las sorprendentes ventajas técnicas logradas mediante la utilización de un comprimido que contenga 150 mg de ácido ibandrónico en el tratamiento de la resorción ósea, frente a la utilización de un comprimido que contenga 2,5 mg de dicho compuesto activo, y que era conocido en el estado de la técnica anterior (numeral 5 del anexo IV).

En consecuencia, me permito manifestar que los documentos técnicos remitidos a ese Despacho junto con el pasado memorial y junto con el presente escrito, sustentan de manera inequívoca el sorprendente aporte al estado de la técnica logrado por el solicitante a través de la información técnica revelada en la invención en cuestión.

- ***"No se encuentran sustentados ejemplos de las formulaciones del medicamento con 100 o 150 mg de principio activo"***

En respuesta a lo anterior, inicialmente resulta de gran importancia resaltar que si bien el ejemplo 1 presentado en la descripción de la solicitud (página 17) hace referencia a un comprimido que contiene 50 mg de ácido ibandrónico (equivalentes a 56.250 mg de la sal monosódica del ácido ibandrónico monohidrato) en combinación con una serie de excipientes que conforman tanto el núcleo como el recubrimiento de dicho comprimido, **a lo largo de la**

descripción también se hace referencia explícita a un medicamento que contiene preferiblemente entre 100 y 150 mg de ácido ibandrónico o una sal farmacéuticamente aceptable del mismo [ver, por ejemplo, las páginas 6 (líneas 14 a 17), 7 (líneas 23 a 25) y 10 (líneas 3 a 6)]. En este sentido, es claro que la presente solicitud sí menciona un medicamento que comprende 100 ó 150 mg de principio activo.

Teniendo en cuenta lo anterior, me permito nuevamente resaltar ante ese Despacho la información técnica revelada en el anexo IV del presente escrito, toda vez que allí se describen plenamente la composición y las características fisicoquímicas y farmacológicas del medicamento revelado en la presente solicitud y que es mundialmente conocido bajo el nombre de BONVIVA, esto es, **se describe completamente un comprimido recubierto por una película, cuyo núcleo contiene 150 mg de ácido ibandrónico mezclado con lactosa, povidona, celulosa microcristalina, crospovidona, ácido esteárico y óxido de silicio, y cuyo recubrimiento está conformado por dióxido de titanio, talco, hipromelosa y magrocol 6000.**

En este sentido, atentamente considero que la información aportada por el solicitante ejemplifica de manera clara y concisa la composición y las características fisicoquímicas y farmacológicas del medicamento revelado en la presente invención, con lo cual se supera completamente la objeción realizada por el señor Examinador a éste respecto.

Reivindicaciones

- ***"La reivindicación 1 se encuentra enunciada por administrado mensualmente" lo cual se refiere a un método de tratamiento"***

Atendiendo a lo anterior, y tal como se mencionó en el numeral 3 del presente memorial, me permito manifestar que el solicitante ha decidido **eliminar** la expresión ***"administrado mensualmente"*** de la reivindicación 1, con lo cual se supera satisfactoriamente la objeción realizada por el señor Examinador a éste respecto.

- ***"La reivindicación 6 se refiere al medicamento de forma general y amplia sin encontrarse plenamente caracterizado, sin encontrarse acorde con lo descrito en el ejemplo 1"***

En respuesta a lo anterior, me permito manifestar que el solicitante ha decidido **eliminar la reivindicación 6 actualmente presentada**, con lo cual se supera completamente la objeción realizada por el señor Examinador a este respecto.

Finalmente, en vista de los argumentos técnicos planteados hasta el momento, y de conformidad con las modificaciones realizadas a la solicitud en cuestión, me permito manifestar que la presente invención cumple a cabalidad con los requisitos de patentabilidad establecidos en los Artículos 28 y 30 de la Decisión 486 de 2000.

5. ANÁLISIS DE LA NOVEDAD Y DEL NIVEL INVENTIVO

De otro lado, el señor Examinador ha objetado la novedad y el nivel inventivo de la presente solicitud con base en las enseñanzas de los siguientes documentos:

- US 6,143,326 **(D1)**
- WO 00/21541 **(D2)**

En este sentido, el señor Examinador argumenta básicamente que en el documento D1 se enseña una formulación que comprende un núcleo de tableta que contiene entre 0.1 a 100 mg de ibandronato y una cubierta libre de ibandronato.

Asimismo, el señor Examinador argumenta que el documento D2 divulga un proceso para la preparación de composiciones farmacéuticas orales que comprenden bisfosfonatos, siendo el ibandronato la sustancia activa preferida, particularmente en una proporción hasta de 50 mg. En este sentido, el señor Examinador también afirma que en los ejemplos 3 y 4 de dicha anterioridad se enseñan formulaciones para tabletas que contienen lactosa, polivinilpirrolidona, celulosa microcristalina, crospovidona, ácido esteárico y dióxido de silicio.

Debido a lo anterior, el señor Examinador concluye que la información técnica revelada en la presente solicitud no es novedosa frente a las enseñanzas de los documentos D1 y D2.

De otro lado, el señor Examinador afirma que para una persona experta en la materia que se base en las enseñanzas de los documentos D1 y D2 sería evidente obtener el medicamento oral de ibandronato monosódico monohidrato en comprimidos recubiertos de 100 mg o 150 mg con los mismos excipientes enseñados en tales anterioridades, por lo que concluye que el problema técnico planteado en la presente solicitud sería resuelto fácilmente por el experto en la materia sin necesidad de emplear habilidad inventiva.

Ahora bien, para responder adecuadamente a dichas objeciones, inicialmente me permito realizar un resumen de las principales enseñanzas de cada una de dichas anterioridades, así como un análisis comparativo detallado entre tales enseñanzas y la materia revelada en la presente solicitud.

5.1 **Consideraciones con respecto al documento US 6'143,326 (D1)**

En términos generales, el documento D1 enseña composiciones farmacéuticas para aplicación oral que contienen ibandronato o una sal fisiológicamente tolerable del mismo.

Específicamente, y de acuerdo con lo establecido por los autores de dicho documento, las formulaciones sólidas enseñadas en D1 comprenden: a) un núcleo que contiene entre 0.1 mg y 100 mg de ibandronato; y, b) un recubrimiento conformado por hidroxipropilmetilcelulosa, polietilenglicol, dióxido de titanio y talco, es decir, un recubrimiento que está libre de ingrediente activo pero que se caracteriza por permitir que éste último sea liberado rápidamente.

5.1.1 **Análisis de la novedad frente a D1**

Con base en lo anterior y con el ánimo de demostrar el inequívoco carácter novedoso que presenta la información técnica revelada en la presente solicitud frente a las enseñanzas del documento D1, a continuación me permito presentar ante ese Despacho las siguientes consideraciones técnicas:

- En primer lugar, resulta de gran importancia mencionar una vez más que de acuerdo con las modificaciones realizadas en el capítulo reivindicatorio de la invención en cuestión (numeral 3 del presente memorial), esta solicitud se encuentra dirigida a proteger un medicamento para administración oral caracterizado porque es un comprimido recubierto por una película, en donde el núcleo del comprimido comprende:

  - 100 mg o 150 mg de un ácido bisfosfónico o una sal farmcéuticamente aceptable del mismo; y

  - uno o mas excipientes farmacéuticamente aceptables seleccionados del grupo conformado por: lactosa, polivinilpirrolidona, celulosa microcristalina, crospovidona, ácido esteárico y dióxido de silicio;

  y en donde el recubrimiento del comprimido comprende uno o más excipientes farmacéuticamente aceptables seleccionados entre el grupo conformado por: hidroxipropil metilcelulosa, dióxido de titanio, talco y polietilenglicol 6000.

- Por su parte, de la atenta lectura del documento D1 es claro que dicha anterioridad enseña, por ejemplo, formulaciones farmacéuticas conformadas por:

  a) un núcleo de tableta que comprende entre 0.1 mg y 100 mg de ibandronato; y

b) un recubrimiento libre de ibandronato que presenta la siguiente composición:

a. alrededor de 51.425% en peso de hidroxipropilmetilcelulosa,
b. alrededor de 24.650% en peso de dióxido de titanio,
c. alrededor de 15.000% en peso de polietilenglicol, y
d. alrededor de 8.925% en peso de talco

Asimismo, tanto en las columnas 3 y 4, como en los ejemplos 1, 2, 3, 4 y 7 del documento D1 se mencionan otros polímeros y adyuvantes que pueden hacer parte del recubrimiento de las formulaciones farmacéuticas allí reveladas. **Sin embargo, es de gran importancia resaltar que a lo largo de dicha anterioridad se enseña claramente que el compuesto activo (ibandronato) NO está mezclado con excipientes o adyuvantes.**

- Ahora bien, de conformidad con lo mencionado en los dos puntos anteriores, es absolutamente claro que el documento D1 **NO** enseña un **comprimido cuyo núcleo está conformado por la mezcla de:**
  - 100 mg ó 150 mg de un ácido bisfosfónico (o una sal farmacéuticamente aceptable del mismo), y
  - uno o más excipientes farmacéuticamente aceptables seleccionados del grupo conformado por: lactosa, polivinilpirrolidona, celulosa microcristalina, crospovidona, ácido esteárico y dióxido de silicio;

  y cuyo recubrimiento esté conformado por uno o más excipientes farmacéuticamente aceptables seleccionados entre el grupo conformado por: hidroxipropil metilcelulosa, dióxido de titanio, talco y polietilenglicol 6000.

Por lo tanto, me permito manifestar que la información técnica revelada en la invención en cuestión presenta un **inequívoco carácter novedoso frente a las enseñanzas del documento D1,** esto es, cumple a cabalidad con las disposiciones de patentabilidad requeridas en el Artículo 16 de la Decisión 486 de 2000.

5.2 Consideraciones con respecto al documento WO 00/21541 (D2)

El documento D2 enseña un proceso para la preparación de composiciones farmacéuticas que contienen bisfosfonatos, el cual está caracterizado básicamente porque la sustancia activa es inicialmente granulada en húmedo por medio de un granulador de lecho fluidizado junto con adyuvantes que no presentan acción abrasiva, y posteriormente es secada, tamizada y procesada para obtener las composiciones farmacéuticas requeridas.

En conexión con lo anterior, resulta de gran importancia resaltar que el objetivo principal de dicha anterioridad era desarrollar un proceso que permitiera reducir las pérdidas de sustancia activa durante el proceso de preparación de composiciones farmacéuticas que contienen no más de 50 mg de bisfosfonatos por unidad de dosis.

5.2.1 **Análisis de la novedad frente a D2**

Con base en lo anterior y con el ánimo de demostrar el inequívoco carácter novedoso que presenta la información técnica revelada en la presente solicitud frente a las enseñanzas del documento D2, inicialmente me permito manifestar que dicha anterioridad no enseña un comprimido cuyo núcleo está conformado por la mezcla de:

- 100 mg ó 150 mg de un ácido bisfosfónico (o una sal farmacéuticamente aceptable del mismo), y

- uno o más excipientes farmacéuticamente aceptables seleccionados del grupo conformado por: lactosa, polivinilpirrolidona, celulosa microcristalina, crospovidona, ácido esteárico y dióxido de silicio;

y cuyo recubrimiento esté conformado por uno o más excipientes farmacéuticamente aceptables seleccionados entre el grupo conformado por: hidroxipropil metilcelulosa, dióxido de titanio, talco y polietilenglicol 6000.

Contrario a esto, el documento D2 únicamente revela un proceso para obtener composiciones farmacéuticas caracterizadas porque comprenden un bajo contenido de ingrediente activo, específicamente, para composiciones farmacéuticas que comprenden hasta 50 mg de ibandronato.

Ahora, teniendo en cuenta los lineamientos establecidos en el Manual Andino de Patentes para llevar a cabo el análisis de la novedad de una solicitud, es claro que un documento puede afectar la novedad de una invención solo si éste contiene explícitamente todas las características técnicas esenciales de la invención bajo estudio, esto es, si dicha anterioridad describe por sí sola todas las características técnicas contenidas en las reivindicaciones analizadas.[1]

Por lo tanto, debido a que dichos requisitos no se cumplen en el presente caso, es claro que **el capítulo reivindicatorio de la presente solicitud de patente es novedoso frente a las enseñanzas del documento D2.**

[1] SECRETARÍA GENERAL DE LA COMUNIDAD ANDINA. Manual para el examen de solicitudes de patentes de invención en las Oficinas de Propiedad Industrial de los Países de la Cumunidad Andina. Lima, Perú; 2004; páginas 65 y 66.

5.3 **Análisis del nivel inventivo de la presente solicitud frente a los documentos D1 y D2**

De otro lado, para demostrar el nivel inventivo que caracteriza a la materia técnica revelada en la presente solicitud frente a las enseñanzas de los documentos D1 y D2, me permito dirigir la atención del señor Examinador hacia las enseñanzas del ANEXO IV remitido a ese Despacho junto con el presente memorial, toda vez que en dicho documento se presentan los datos experimentales que demuestran el sorprendente efecto técnico logrado con los medicamentos revelados en la presente invención durante el tratamiento de la resorción ósea.

Específicamente, tanto en dicho compendio (ANEXO IV) como en los documentos remitidos a ese Despacho junto con la respuesta dada al Concepto Técnico anterior, se revelan, -por ejemplo-, los resultados de un estudio realizado por el solicitante y que es conocido bajo el nombre de MOBILE (Monthly Oral iBandronate In LadiEs); dicho estudio consistió básicamente de la realización de un ensayo clínico durante dos años, aleatorizado y doble ciego con 1.609 mujeres con osteoporosis postmenopáusica, con el cual se comparó la eficacia y seguridad de diferentes dosis mensuales orales de ibandronato (100mg en un solo día; 100mg separados en dosis de 50mg durante dos días consecutivos o 150mg en un solo día) con el régimen diario oral (2.5mg) aprobado actualmente por la FDA y la Unión Europea.

Dicho estudio permitió concluir que la gran mayoría de mujeres cuyo régimen de tratamiento contra la resorción ósea consistió en el consumo mensual de un comprimido con 100 mg o 150 mg de ibandronato lograron incrementos significativos en la densidad mineral ósea tanto en la espina lumbar (LS BMD), como en la cadera (HT BMD). Así, por ejemplo, de acuerdo a los datos revelados en los documentos previamente mencionados, es claro que un 91.3% de pacientes a las que se les administró mensualmente 150 mg de ibandronato mostraron un aumento en la densidad mineral ósea de la espina lumbar (LS BMD), mientras que sólo un 84% de pacientes a quienes se les administró diariamente 2.5 mg de ibandronato mostraron un aumento en LS BMD. Asimismo, un mayor porcentaje de pacientes a las que se les administró mensualmente 100 mg (87.1%) y 150 mg (90.0%) de ibandronato lograron aumentos substanciales en la densidad mineral ósea en la cadera (TH BMD), pues sólo un 76.7% de pacientes a las que se les administró diariamente 2.5 mg de ibandronato lograron incrementos similares en TH BMD.

Aparte de lo anterior, el medicamento revelado en la presente solicitud también representa un importante avance en el estado de la técnica si se tiene en cuenta que para la gran mayoría de los pacientes el consumo diario de un medicamento que contiene 2,5 mg de ácido ibandrónico resulta inconveniente, lo que ocasionaba que hasta dos tercios de las pacientes abandonaran el tratamiento de la osteoporosis luego de un año, quedándose sin

los beneficios de la reconstrucción del hueso que estos fármacos sólo pueden proporcionar al cabo del tiempo.

Por todo lo anterior, atentamente me permito manifestar ante ese Despacho que el novedoso medicamento revelado en la solicitud de patente en cuestión presenta un inequívoco carácter inventivo frente a las enseñanzas de los documentos D1 y D2, toda vez **que una persona experta en la materia técnica en cuestión no encuentra en dichas anterioridades enseñanza alguna que le sugiera un medicamento de administración mensual que comprenda 100 ó 150 mg de ibandronato (o una sal farmacéuticamente aceptable del mismo) junto con excipientes farmacéuticamente aceptables**. Asimismo, es claro que la persona experta en la materia tampoco encontraría obvio el medicamento de la solicitud de patente en cuestión, debido a que éste no habría podido sugerir las notables ventajas técnicas y terapéuticas obtenidas a partir de dicha novedosa composición, tal como se ha comentado previamente en el presente memorial.

6. CONCLUSIÓN

Teniendo en cuenta las modificaciones realizadas en la descripción y en el capítulo reivindicatorio de la presente solicitud, y de conformidad con los argumentos técnicos presentados para demostrar el inequívoco carácter novedoso e inventivo de dicho nuevo capítulo reivindicatorio frente a las enseñanzas de los documentos D1 y D2, es completamente claro que se han superado todas las objeciones expuestas por el señor Examinador en contra de la patentabilidad de la presente invención, y por lo tanto, dicha solicitud es merecedora del privilegio de patente solicitado.

7. Anexo al presente memorial me permito presentar:

i) Recibo número 08-84,532, expedido por la Superintendencia de Industria y Comercio, que acredita el pago de las modificaciones mencionadas;

ii) Copia de las páginas 1-17 de la descripción, en la cual se ha realizado la modificación previamente mencionada;

iii) Copia del nuevo capítulo reivindicatorio compuesto por 5 reivindicaciones, el cual reemplaza al capítulo actualmente presentado y en el que se han realizado las modificaciones previamente mencionadas; y

iv) Copia del compendio electrónico para el medicamento denominado: *"Bonviva 150 mg Film-Coated Tablets".*

8. En vista de todo lo anterior, ruego a usted proceder a estudiar nuevamente la solicitud a la luz de las argumentaciones presentadas y de las modificaciones realizadas y conceder el privilegio de patente solicitado.

Señor Superintendente,

ALICIA LLOREDA RICAURTE

T.P. 53.215

NOTARIA SEXTA DE BOGOTA
RECONOCIMIENTO Y PRESENTACION PERSONAL
Bogotá, D.C. 04 NOV 2008
Ante mi AMPARO QUINTERO ARTURO,
NOTARIA SEXTA DEL CÍRCULO DE
BOGOTÁ D.C.
Compareció(eron) Alicia Lloreda Ricaurte
Quien(es) exhibió(eron) la(s) C.C. 39690713
y declaró(aron) que la(s) firma(s) que aparece(n) en el presente documento es(son) la(s) suya(s) y que el contenido del mismo es cierto.
En constancia se firma esta diligencia.

NOTARIA SEXTA BOGOTA, D.C.
CODEX JURIS CIVILIS

ALICIA LLOREDA RICAURTE

C.C. No. 39.690.713 de Usaquén

REPUBLICA DE COLOMBIA
Amparo Quintero Arturo
NOTARIA
NOTARÍA SEXTA DE BOGOTÁ

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 84,532
FECHA : OCTUBRE 27 DE 2008

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
LLOREDA Y CIA S. A	CONSIGNACION	BANCO DE BOGOTA	062754387	80211740	27/10/2008	9,353,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO		TOTAL CONCEPTO
1	50005-01-03 CAMBIO DE MODALIDAD Y MODIFICA	12	MARCAS Y LEMAS COMERCIALES	103,000.00
			TOTAL : $	103,000.00

SON: CIENTO TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

F. Hoffmann la Roche Ag

Exp. 04-096.462 153

ACIDO BISFOSFONICO PARA EL TRATAMIENTO Y PREVENCION DE OSTEOPOROSIS

RESUMEN-OBJETO Y FINALIDAD DE LA INVENCION

La presente invención se refiere al empleo de los ácidos bisfosfönicos o las sales farmacéuticamente aceptables de los mismos, para la elaboración de medicamentos para la prevención o tratamiento de transtornos caracterizados por un aumento patológico de la resorción ósea, especialmente para la prevención y tratamiento de la osteoporosis.

*****

ACIDO BISFOSFONICO PARA EL TRATAMIENTO Y PREVENCION DE *OSTEOPOROSIS*

La presente invención se refiere al empleo de los ácidos bisfosfónicos, especialmente del ácido (1-hidroxi-3-(N-metil-N-pentil)aminopropiliden-1,1,bisfosfónico (ácido ibandrónico) o las sales farmacéuticamente aceptables de los mismos, para la elaboración de medicamentos para la prevención o tratamiento de transtornos caracterizados por un aumento patológico de la resorción ósea, especialmente para la prevención y tratamiento de la osteoporosis.

Los huesos sirven principalmente como de soporte, y en consecuencia el hueso es contemplado con frecuencia como un simple material de construcción. Sin embargo, el hueso es un complicado biomaterial adaptado para una amplia variedad de necesidades, estímulos y agentes nocivos a los cuales está expuesto. Se dispone de endoprótesis como substitutos de huesos y articulaciones. Sin embargo, las endoprótesis aún cuando biomecánicamente son altamente refinadas, no tienen un efecto activo sobre el entorno ni en factores de carga.

Una variedad de transtornos en humanos y mamíferos implican o están asociados con la anormal resorción ósea. Estos desórdenes incluyen aunque no están limitados por ellas, la osteoporosis, la enfermedad de Paget, la pérdida periprostética de hueso u osteolisis, y la hipercalcemia de la enfermedad maligna y metastásica de los huesos. La más común de estas enfermedades es la osteoporosis, la cual en su manifestación más frecuente tiene lugar en las mujeres postmenopáusicas. Debido a que la osteoporosis así como otros transtornos asociados con la pérdida ósea, son condiciones

crónicas, se cree que la terapia adecuada requerirá generalmente un tratamiento crónico.

Los bisfosfonatos, a saber, los ácidos bisfosfónicos o las sales farmacéuticamente aceptables de los mismos, son compuestos sintéticos análogos del pirofosfato, que se encuentra en estado natural. Debido a su acusada afinidad para el fosfato de calcio en fase sólida, los bisfosfonatos se unen fuertemente al mineral del hueso. Los bisfosfonatos farmacológicamente activos son ya bien conocidos en la técnica y son potentes inhibidores de la resorción ósea y son por lo tanto de utilidad en el tratamiento y prevención de enfermedades que implican una resorción ósea anormal, especialmente la osteoporosis, la enfermedad de Paget, la hipercalcemia de malignidades y enfermedades metastásicas y metabólicas de los huesos.

Los bisfosfonatos como agentes farmacéuticos están descritos por ejemplo en las patentes EP-A-170.228, EP-A-197.478, EP-A-22.751, EP-A-252.504, EP-A-252.505, EP-A-258.618, EP-A-350.002, EP-A-273.190, WO-A-90/00798, etc., cada una de las cuales está incorporada a la presente como referencia.

Las formas farmacéuticas de los bisfosfonatos que se encuentran corrientemente en el mercado son formulaciones orales (comprimidos o cápsulas) o soluciones para la inyección o infusión intravenosa. Son sistémicamente bien tolerados cuando se administran a dosis terapéuticas. Sin embargo, los bisfosfonatos en su conjunto son irritantes para la piel y membranas mucosas, y cuando se añaden por vía oral

sobre una base continuada, pueden ocasionar efectos secundarios en el tracto digestivo, p. ej., episodios adversos o transtornos gastrointestinales. En consecuencia y debido a su baja biodisponibilidad oral, la ruta oral de administración ha sido hasta la fecha poco recomendada para emplear en pacientes.

Los bisfosfonatos pueden clasificarse en dos grupos con diferentes modos de acción. El ibandronato pertenece a los bisfosfonatos más potentes que contienen nitrógeno [Russell 1999 Russell RGG, Rogers ML]. Bisphosphonates: From the laboratory to the clinic and back again" ("Bisfosfonatos: Del laboratorio a la clínica y regreso"). Bone ("Hueso") 25 (1): 97-106 (1999); Rogers MJ, Gordon S, Benford HL, Coxon FP, Luckman SP, Monkkonen J, Frith JC. "Cellular Molecular mechanisms of action of bisphosphonates" ("Mecanismos moleculares celulares de acción de los bisfosfonatos"). Cancer ("Cáncer") 88 (12) Suppl: 2961-2978 (2000)]. El ibandronato es uno de los bisfosfonatos más potentes actualmente en desarrollo clínico en la osteoporosis y enfermedades metastásicas de los huesos. En modelos animales de resorción ósea, el ibandronato es 2, 10, 50 y 500 veces más potente que el risedronato, alendronato, pamidronato y clodronato respectivamente [Mühlbauer R.C.,F. Bauss, R. Schenk, M. Janner, E. Bosies, K. Strein y H. Fleisch. "BM 21.0955 a potent new bisphosphonate to inhibit bone resorption" ("BM 21.0955, un potente nuevo bisfosfonato para la inhibición de la resorción ósea"). J. Bone Miner. Res. 6: 1003 - 1001 (1991)].

El ibandronato inhibe la resorción ósea sin perjudicar la mineralización (Mühlbauer y col., Mühlbauer R.C., F. Bauss, R. Schenk, M. Janner, E. Bosies, K. Strein, y H. Fleisch. "BM 21.0955 a potent new bisphosphonate to inhibit bone resorption" ("BM 21.0955, un potente nuevo bisfosfonato para la inhibición de la resorción ósea"). J. Bone Miner. Res. 6: 1003 - 1011 (1991).). Se ha demostrado que disminuye la actividad osteoclástica con lo cual inhibe la destrucción de los huesos. A dosis altas reduce también el número de osteoclastos (Mühlbauer y col., Mühlbauer R.C., F. Bauss, R. Schenk, M. Janner, E. Bosies, K. Strein y H. Fleisch. "BM 21.0955 a potent new bisphosphonate to inhibit bone resorption" ("BM 21.0955, un potente nuevo bisfosfonato para la inhibición de la resorción ósea"). J. Bone Miner. Res. 6: 1003 - 1011 (1991)).

Como se ha descrito, los bisfosfonatos son aceptados por proporcionar una fuerte eficacia en el control de la osteoporosis. Sin embargo, dadas las restricciones de administración relacionadas con la baja biodisponibilidad oral y potenciales efectos gastro intestinales, existe una clara oportunidad para los regímenes que ofrecen una mejor comodidad y flexibilidad, conduciendo a un nivel más alto de aceptación y un superior control/satisfacción del paciente. Se han descrito en la técnica regímenes intermitentes como por ejemplo, la administración una vez a la semana, pero dichos tratamientos intermitentes no proporcionan el resultado deseado.

Se ha descubierto ahora que la prevención o el

tratamiento de transtornos caracterizados por un aumento patológico de la resorción ósea como p. ej., la osteoporosis, pueden ser mejorados mediante la administración mensual de 50 a 250 mg de un bisfosfonato o una sal farmacéuticamente aceptable del mismo, especialmente mediante una administración mensual de ibandronato, es decir, ácido ibandrónico o una sal farmacéuticamente aceptable del mismo.

La presente invención se refiere por lo tanto al empleo de un ácido bisfosfónico o una sal farmacéuticamente aceptable del mismo, particularmente con el empleo del ácido ibandrónico o una sal farmacéuticamente aceptable del mismo, para la preparación de medicamentos para la prevención o tratamiento de trastornos caracterizados por un aumento patológico de la resorción ósea, en donde el medicamento:

a) contiene aproximadamente de 50 a 250 mg, de preferencia aproximadamente 100 a 150 mg de un ácido bisfosfónico o una sal farmacéuticamente aceptable del mismo, y

b) el medicamento se administra por vía oral en uno, dos o tres días consecutivos por mes.

El tratamiento por vía oral mensual, mediante la administración de por lo menos el 120%, especialmente del 120% al 200% de la dosis prevista, ofrece mayores ventajas para el paciente con respecto a la comodidad y aceptación así como superiores resultados. La "dosis prevista" (100%) corresponde a las dosis diarias eficaces acumuladas. Antes de completar el programa de desarrollo clínico del ibandronato, ningún bisfosfonato había demostrado prospectivamente una

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eficacia en la reducción de fracturas con un intervalo sin fármaco, fuera de la administración diaria. En resumen, es completamente inesperado que el beneficio de la reducción de fracturas pueda derivarse de una administración mensual de un bisfosfonato con un esquema de administración de un comprimido único o de varios comprimidos.

En consecuencia, la presente invención se refiere al empleo de ácidos bisfosfónicos o sales farmacéuticamente aceptables de los mismos para la elaboración de un medicamento para la prevención o tratamiento de transtornos caracterizados por un aumento patológico de la resorción ósea, p. ej., la osteoporosis, en donde el medicamento contiene por lo menos el 120% de la dosis diaria eficaz prevista, de ácidos bisfosfónicos o sales farmacéuticamente aceptables de los mismos, y se administra en uno, dos o tres días consecutivos por mes.

Con más preferencia, la invención comprende el empleo del ácido ibandrónico o las sales farmacéuticamente aceptables del mismo, para la elaboración de un medicamento para la prevención o tratamiento de transtornos caracterizados por un aumento patológico de la resorción ósea en donde el medicamento,

a) contiene aproximadamente de 100 a aproximadamente 150 mg de ácido ibandrónico o una sal farmacéuticamente aceptable del mismo, y

b) se administra por vía oral en uno, dos o tres días consecutivos por mes.

El término "ácido bisfosfónico" significa compuestos

caracterizados por dos grupos fosfónicos unidos por enlaces fosfoéter a un átomo de carbono central (geminal). Esta estructura P-C-P está ejemplificada en la fórmula I de más adelante. Debe tenerse en cuenta que el término "ácidos bisfosfónicos" como se emplea en la presente cuando se refiere a los agentes terapéuticos de la presente invención, se emplea también para abarcar los bisfosfonatos, los ácidos bifosfónicos y los ácidos bisfosfónicos, así como también las sales y derivados de estos materiales. El empleo de una nomenclatura específica al referirse al bisfosfonato o bisfosfonatos no significa que se limita el ámbito de la presente invención, a no ser que esté específicamente indicado.

El término "farmacéuticamente aceptable" como se emplea en la presente, significa que las sales o agentes quelantes son aceptables desde el punto de vista de la toxicidad.

El término "sal farmacéuticamente aceptable", se refiere a las sales de amonio, sales de metal alcalino tales como potasio y sodio (incluyendo las sales mono, di y trisódicas que son las preferidas), sales de metal alcalinotérreo tales como las sales de calcio y de magnesio, con bases orgánicas, como p. ej., las sales de diciclohexilamina, N-metil-D-glucamina y sales con aminoácidos tales como la arginina, lisina, etc.

El término "transtornos caracterizados por un aumento patológico de la resorción ósea" se refiere a las condiciones definidas médicamente con o sin causa identificable (tal como una osteoporosis menopáusica, osteoporosis

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juvenil idiopática, osteoporosis asociada con el síndrome de Klinefelter, osteoporosis masculina, osteoporosis debido a factores nutricionales, osteoporosis relacionada con el trasplante de un órgano, osteoporosis asociada con la inmovilización, condición inflamatoria y la osteoporosis inducida por corticosteroides).

El término "uno, dos o tres días consecutivos por mes" significa la administración de comprimidos proporcionales de una a tres dosis, o no proporcionales a ninguna dosis, en uno, dos o tres días consecutivos del mes, de preferencia un día por mes. Como se emplea en la presente, el término "mes" se emplea de acuerdo con el significado generalmente empleado de una medida del tiempo que comprende aproximadamente cuatro (4) semanas, aproximadamente 30 días, o aproximadamente 1/12 de un año natural.

El término "medicamento" se refiere a una composición farmacéutica. El término abarca los esquemas de administración simple o múltiple.

De preferencia el medicamento se administra una vez al mes. De preferencia el medicamento se administra como dosis única, aunque el ámbito de la presente invención incluye medicamentos administrados como subdosis múltiples como p. ej., en dos días consecutivos por mes o tres días consecutivos por mes.

De preferencia, el medicamento comprende por lo menos el 100%, de preferencia del 120% al 200%, con más preferencia del 120 al 150% de la dosis eficaz de ácidos bisfosfónicos o sales farmacéuticamente aceptables de los mismos, con más

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preferencia del ácido ibandrónico o sales farmacéuticamente aceptables del mismo.

El término "dosis eficaz" se refiere aproximadamente de 50 a aproximadamente 250 mg, con más preferencia de aproximadamente 100 a aproximadamente 150, de un bisfosfonato o sales farmacéuticamente aceptables del mismo, por ejemplo de ácido ibandrónico o una sal farmacéuticamente aceptable del mismo. Como se ha indicado, la dosis eficaz puede ser una dosis simple o múltiples subdosis. Por ejemplo si la dosis eficaz es de 150 mg, la dosis puede ser una (1) dosis de 150 mg, dos (2) subdosis de 75 mg administradas en un día o en dos días consecutivos, o tres (3) subdosis de 50 mg administradas en un día o en dos o tres días consecutivos, si la dosis eficaz es de 100 mg, la dosis puede incluir una (1) dosis de 100 mg, dos (2) subdosis de 50 mg administradas en un día o dos días consecutivos, de preferencia en dos días consecutivos.

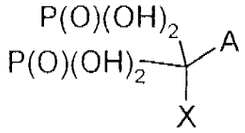
"Acidos bisfosfónicos y sales farmacéuticamente aceptables de los mismos" como agentes farmacéuticos, están descritos por ejemplo en las patentes US nºs 4.509.612, 4.666.895, 4719.203, 4.777.163, 5.002.937, 4.971.958 y 4.958.839 y en las solicitudes de patente europea nºs 252.504 y 252.505, incorporadas a la presente como referencias para la descripción.

Métodos para la preparación de ácidos bisfosfónicos y sales farmacéuticamente aceptables de los mismos, pueden encontrarse p. ej., en las patentes U.S. nºs 3.962.432, 4.054.598, 4.267.108, 4.327.039, 4.407.761, 4.621.077,

4.624.947, 4.746.654, 4.922.077, 4.970.335, 5.019.651, 4.761.406, 4.876.248; en J. Org. Chem. 32, 4111 (1967) y en la solicitud de patente europea 252.504, incorporadas a la presente como referencia. Las sales farmacéuticamente aceptables de los ácidos bisfosfónicos pueden también emplearse en la presente invención. Ejemplos de sales básicas de ácidos bisfosfónicos incluyen las sales de amonio, sales de metal alcalino como potasio y sodio (incluyendo las sales mono, di y trisódicas) (las cuales son las preferidas), sales de metal alcalinotérreo tales como calcio y magnesio, sales con bases orgánicas tales como las sales de diciclohexilamina, N-metil-D-glucamina y sales con aminoácidos tales como la arginina, lisina, etcétera. Se prefieren las sales no tóxicas, fisiológicamente aceptables. Las sales pueden prepararse por métodos ya conocidos en la técnica, como se describen en la solicitud de la patente europea 252.504 ó en la patente US n° 4.922.077, incorporadas a la presente como referencia.

De preferencia, el medicamento contiene de 100 a 150 mg de un ácido ibandrónico o de una sal farmacéuticamente aceptable del mismo. De preferencia, el medicamento se administra como dosis simple.

En una versión preferida de la presente invención, el término "bisfosfonato" de la presente invención corresponde a compuestos de fórmula general



(I)

en donde A y X son independientemente entre sí, seleccionadas del grupo formado por hidrógeno, hidroxilo, halógeno, amino, SH, fenilo, alquilo, mono o dialquilamino, mono o dialquilaminoalquilo, alcoxilo, tioalquilo, tiofenilo, y conjuntos arilo o heteroarilo seleccionados del grupo formado por fenilo, piridilo, furanilo, pirrolidinilo, imidazolilo y bencilo, en donde el conjunto arilo o heteroarilo está opcionalmente substituido con alquilo.

En la fórmula química anterior, A puede incluir X, y X incluye A de forma que los dos conjuntos pueden formar parte de la misma estructura cíclica.

La fórmula química anterior pretende abarcar estructuras carbocíclicas, aromáticas y heteroaromáticas para los substituyentes A y/o X, p. ej., naftilo, quinolilo, isoquinolilo, adamantilo y clorofeniltio.

Estructuras preferidas son aquellas en las cuales A se selecciona del grupo formado por hidrógeno, hidroxilo y halógeno, y X se selecciona del grupo formado por alquilo, halógeno, tiofenilo, tioalquilo y dialquilaminoalquilo.

Las estructuras más preferidas son aquellas en las cuales A se selecciona del grupo formado por hidrógeno, hidroxilo y Cl, y X se selecciona del grupo formado por alquilo, Cl, clorofeniltio y dialquilaminoalquilo.

El ácido bisfosfónico preferido o su sal farmacéuticamente aceptable, se selecciona del grupo formado por alendronato, cimadronato, clodronato, EB-1053, tiludronato, etidronato, ibandronato, incadronato, minodronato, neridronato, olpadronato, risedronato, piridronato, pamidro-

nato, zolendronato o sales aceptables de los mismos, p. ej., la sal monosódica del ácido ibandrónico monohidrato.

El ácido ibandrónico (ácido 1-hidroxi-3-(N-metil-N-pentil)aminopropiliden-1,1-bisfosfónico) o las sales compatibles del mismo son particularmente preferidas, p. ej., la sal monosódica del ácido ibandrónico monohidrato.

Los bisfosfonatos y las sales farmacéuticamente aceptables, pueden administrarse solas o en combinación con otros fármacos activos para huesos, bien en combinaciones fijas o bien separadas tanto físicamente como en el tiempo, incluyendo hormonas tales como una hormona esteroide, p. ej., un estrógeno, un agonista parcial de estrógeno, o una combinación estrógeno-gestágeno; una calcitonina o análogo o derivado de la misma, p. ej., la hormona del salmón, de la anguila o la hormona del paratiroides calcitonina humana o análogos de las mismas, p. ej., PTH (1-84), PTH (1-34), PTH (1-36). PTH (1-38), PTH (1-31)NH2 o PPTS 893; un SERM (Selective Estrogen Receptor Modulator) ("Modulador receptor de estrógeno selectivo"), p. ej., raloxifene, lasofoxifene, TSE-434, FC1271, tibolone, vitamina D ó un análogo. Estos fármacos activos para el hueso adicionales, pueden administrarse más frecuentemente que el bisfosfonato.

Composiciones farmacéuticas apropiadas son ya conocidas en la especialidad y han sido descritas p. ej., en las patentes US nºs 6.143.326 y 6.294.196, las cuales se incorporan a la presente como referencia.

Para la preparación de comprimidos, comprimidos lacados, grageas o cápsulas de gelatina dura, los compuestos de la

presente invención pueden mezclarse con excipientes inorgánicos u orgánicos farmacéuticamente inertes. Ejemplos de excipientes adecuados para comprimidos, grageas o cápsulas de gelatina dura incluyen la lactosa, almidón de maíz o derivados de los mismo, talco o ácido esteárico o sales del mismo.

Las composiciones farmacéuticas pueden contener también agentes conservantes, agentes solubilizantes, agentes estabilizantes, agentes humectantes, emulsionantes, edulcorantes, colorantes, odorantes, sales para variar la presión osmótica, tampones, agentes para recubrimiento o antioxidantes. Pueden contener también otros agentes terapéuticemente valiosos. De preferencia, la composición farmacéutica es un comprimido recubierto con una película en el cual el núcleo del comprimido contiene 50 a 200 mg de un ácido bisfosfónico o una sal del mismo farmacéuticamente aceptable como se ha definido más arriba y uno o más excipientes farmacéuticamente aceptables seleccionados del grupo formado por lactosa, polivinilpirrolidona, celulosa microcristalina, crospovidona, ácido esteárico, dióxido de silicio y el recubrimiento del comprimido contiene uno o más excipientes farmacéuticamente aceptable seleccionados del grupo formado por hidroxipropilmetilcelulosa, dióxido de titanio, talco y polietilenglicol 6000. Estas composiciones son ya conocidas en la especialidad y están descritas por ejemplo en las patentes US n^{os} 6.143.326 y 6.294.196.

Otro aspecto de la presente invención es un método para el tratamiento, reducción o prevención de trastornos carac-

terizados por un aumento patológico de la resorción ósea, el cual comprende la administración a un mamífero de una cantidad efectiva de ácidos bisfosfónicos o sales aceptables de los mismos. Particularmente, la invención se refiere a un método para el tratamiento, reducción o prevención de transtornos caracterizados por un aumento patológico de la resorción ósea, el cual comprende la administración oral de una cantidad efectiva de un ácido bisfosfónico o una sal farmacéuticamente aceptable del mismo, en donde se administra aproximadamente de 50 a 250 mg de ácido bisfosfónico o una sal farmacéuticamente aceptable del mismo, y se administra en uno, dos o tres días consecutivos por mes. Como se ha indicado más arriba, la cantidad efectiva de ácido bisfosfónico o sal farmacéuticamente aceptable del mismo puede administrarse en forma de dosis simple o como subdosis múltiples.

De preferencia, el método comprende la administración de aproximadamente 50 a 250 mg, de preferencia aproximadamente 100 a 150 mg, de un bisfosfonato o una sal farmacéuticamente aceptable del mismo, dos o tres días consecutivos por mes. Aunque el método incluye la administración de la dosis mediante subdosis múltiples, el método aboga de preferencia por una dosis simple: Ejemplos para la administración de la dosis mediante subdosis múltiples son como sigue: si la dosis eficaz es de 150 mg. la dosis puede ser dos (2) subdosis de 75 mg administradas en un día o dos días consecutivos, o tres (3) subdosis de 50 mg administradas en un día o en dos o tres días consecutivos; si la dosis eficaz es de 100 mg, la dosis

puede ser dos (2) subdosis de 50 mg administradas en un día o dos días consecutivos, de preferencia en dos días consecutivos. El bisfosfonato preferido es el ibandronato o una sal farmacéuticamente aceptable del mismo, p. ej., la sal monosódica del ácido ibandrónico monohidrato.

De preferencia, en el método de acuerdo con la presente invención, el ácido bisfosfónico se selecciona del grupo formado por alendronato, cimadronato, clodronato, EB-1053, tiludronato, etidronato, ibandronato, incadronato, minodronato, neridronato, olpadronato, risedronato, piridronato, pamidronato, zolendronato o sales farmacéuticamente aceptables de los mismos. Con más preferencia el ácido bisfosfónico es el ibandronato o una sal farmacéuticamente aceptable del mismo, p. ej., la sal monosódica del ácido ibandrónico, monohidrato.

La invención se describe a continuación con referencia a las versiones ejemplificadas.

EJEMPLOS

EJEMPLO 1: Composición farmacéutica

El ejemplo muestra la composición de un comprimido de 50 mg. La composición y preparación de estos comprimidos ya son conocidas en la especialidad y están descritas por ejemplo en las patentes US nºs 6.143.326 y 6.294.196.

Pueden prepararse otras composiciones ajustando los ingredientes de acuerdo con la cantidad de bisfosfonato, p. ej., la sal monosódica del ácido ibandrónico monohidrato.

Comprimido de 50 mg recubierto con una película	
Componentes	**mg por comprimido**
Núcleo del comprimido:	
Sal monosódica del ácido ibandrónico, monohidrato	56.250
Lactosa monohidrato	92.750
Povidona K 25	5.000
Celulosa microcristalina	30.000
Crospovidona	10.000
Acido esteárico purificado	4.000
Dióxido de silicio coloidal	2.000
Recubrimiento del comprimido:	
Hidroxipropilmetilcelulosa	5.1425
Dióxido de titanio	2.4650
Talco	0.8925
Polietilenglicol 6.000	1.5000
Peso final:	**210.000**

REIVINDICACIONES

1. Un medicamento para administración oral caracterizado porque es un comprimido recubierto por una película, en donde el núcleo del comprimido comprende:

- 100 mg o 150 mg de un ácido bisfosfónico o una sal farmcéuticamente aceptable del mismo; y,
- uno o mas excipientes farmacéuticamente aceptables seleccionados del grupo conformado por: lactosa, polivinilpirrolidona, celulosa microcristalina, crospovidona, ácido esteárico y dióxido de silicio;

y en donde el recubrimiento del comprimido comprende uno o mas excipientes farmacéuticamente aceptables seleccionados entre el grupo conformado por: hidroxipropil metilcelulosa, dióxido de titanio, talco y polietilenglicol 6000.

2. El medicamento de la reivindicación 1, en donde el ácido bisfosfónico es el ácido ibandrónico o una sal farmacéuticamente aceptable del mismo.

3. El medicamento de las reivindicaciones 1 y 2, el cual comprende 100 mg de ácido bisfosfónico o una sal farmacéuticamente aceptable del mismo.

4. El medicamento de las reivindicaciones 1 y 2, el cual comprende 150 mg de ácido bisfosfónico o una sal farmacéuticamente aceptable del mismo.

5. El medicamento de acuerdo con cualquiera de las reivindicaciones 1 a 4, en donde el ácido bisfosfónico o la sal farmacéuticamente aceptable del mismo es la sal monosódica del ácido ibandrónico monohidrato.

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Bonviva 150mg Film-Coated Tablets ■

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1. NAME OF THE MEDICINAL PRODUCT

Bonviva ▼150 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 150 mg ibandronic acid (as ibandronic sodium monohydrate).

Excipients

Each film-coated tablet contains 162.75 mg lactose monohydrate. For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

White to off white film-coated tablets, of oblong shape marked "BNVA" on one side, and "150" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of osteoporosis in postmenopausal women at increased risk of fracture (see section 5.1).

A reduction in the risk of vertebral fractures has been demonstrated, efficacy on femoral neck fractures has not been established.

4.2 Posology and method of administration

For oral use.

The recommended dose is one 150 mg film-coated tablet once a month. The tablet should preferably be taken on the same date each month.

Bonviva should be taken after an overnight fast (at least 6 hours) and 1 hour before the first food or drink (other than water) of the day (see section 4.5) or any other oral medicinal products or supplementation (including calcium):

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• Tablets should be swallowed whole with a glass of plain water (180 to 240 ml) while the patient is sitting or standing in an upright position. Patients should not lie down for 1 hour after taking Bonviva.

• Plain water is the only drink that should be taken with Bonviva. Please note that some mineral waters may have a higher concentration of calcium and therefore, should not be used.

• Patients should not chew or suck the tablet, because of a potential for oropharyngeal ulceration.

In case a dose is missed, patients should be instructed to take one Bonviva 150 mg tablet the morning after the tablet is remembered, unless the time to the next scheduled dose is within 7 days. Patients should then return to taking their dose once a month on their originally scheduled date.

If the next scheduled dose is within 7 days, patients should wait until their next dose and then continue taking one tablet once a month as originally scheduled.

Patients should not take two tablets within the same week.

Patients should receive supplemental calcium and / or vitamin D if dietary intake is inadequate (see section 4.4 and section 4.5).

Patients with renal impairment

No dosage adjustment is necessary for patients with mild or moderate renal impairment where creatinine clearance is equal or greater than 30 ml/min.

Bonviva is not recommended for patients with a creatinine clearance below 30 ml/min due to limited clinical experience (see section 4.4 and section 5.2).

Patients with hepatic impairment

No dosage adjustment is required (see section 5.2).

Elderly

No dosage adjustment is required (see section 5.2).

Children and adolescents

There is no experience in children.

4.3 Contraindications

- Hypocalcaemia (see section 4.4)

- Hypersensitivity to ibandronic acid or to any of the excipients.

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4.4 Special warnings and precautions for use

Hypocalcaemia must be corrected before starting Bonviva therapy. Other disturbances of bone and mineral metabolism should also be effectively treated. Adequate intake of calcium and vitamin D is important in all patients.

Bisphosphonates have been associated with dysphagia, oesophagitis and oesophageal or gastric ulcers. Therefore patients, especially those with a history of prolonged oesophageal transit time, should pay particular attention to and be able to comply with the dosing instructions (see section 4.2).

Physicians should be alert to signs or symptoms signalling a possible oesophageal reaction during therapy, and patients should be instructed to discontinue Bonviva and seek medical attention if they develop symptoms of oesophageal irritation such as new or worsening dysphagia, pain on swallowing, retrosternal pain, or heartburn.

Since NSAIDS and bisphosphonates are both associated with gastrointestinal irritation, caution should be taken during concomitant administration.

Due to limited clinical experience, Bonviva is not recommended for patients with a creatinine clearance below 30 ml/min (see section 4.2 and section 5.2).

Osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection (including osteomyelitis) has been reported in patients with cancer receiving treatment regimens including primarily intravenously administered bisphosphonates. Many of these patients were also receiving chemotherapy and corticosteroids. Osteonecrosis of the jaw has also been reported in patients with osteoporosis receiving oral bisphosphonates.

A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g. cancer, chemotherapy, radiotherapy, corticosteroids, poor oral hygiene).

While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop osteonecrosis of the jaw while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis of the jaw. Clinical judgement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Drug-Food Interactions

Oral bioavailability of ibandronic acid is generally reduced in the presence of

food. In particular, products containing calcium and other multivalent cations (such as aluminium, magnesium, iron), including milk, are likely to interfere with absorption of Bonviva, which is consistent with findings in animal studies. Therefore, patients should fast overnight (at least 6 hours) before taking Bonviva and continue fasting for 1 hour following intake of Bonviva.

Drug-Drug Interactions

Calcium supplements, antacids and some oral medicinal products containing multivalent cations (such as aluminium, magnesium, iron) are likely to interfere with the absorption of Bonviva. Therefore, patients should not take other oral medicinal products for at least 6 hours before taking Bonviva and for 1 hour following intake of Bonviva. Pharmacokinetic interaction studies in postmenopausal women have demonstrated the absence of any interaction potential with tamoxifen or hormone replacement therapy (oestrogen). No interaction was observed when co-administered with melphalan/prednisolone in patients with multiple myeloma.

In healthy male volunteers and postmenopausal women, intravenous administration of ranitidine caused an increase in ibandronic acid bioavailability of about 20 %, probably as a result of reduced gastric acidity. However, since this increase is within the normal variability of the bioavailability of ibandronic acid, no dosage adjustment is considered necessary when Bonviva is administered with H2-antagonists or other active substances which increase gastric pH.

Metabolic interactions are not considered likely, since ibandronic acid does not inhibit the major human hepatic P450 isoenzymes and has been shown not to induce the hepatic cytochrome P450 system in rats. Furthermore, plasma protein binding is approximately 85 % - 87 % (determined *in vitro* at therapeutic drug concentrations), and thus there is a low potential for drug-drug interaction due to displacement. Ibandronic acid is eliminated by renal excretion only and does not undergo any biotransformation. The secretory pathway appears not to include known acidic or basic transport systems involved in the excretion of other active substances.

In a two-year study in postmenopausal women with osteoporosis (BM 16549), the incidence of upper gastrointestinal events in patients concomitantly taking aspirin or NSAIDs was similar in patients taking Bonviva 2.5 mg daily or 150 mg once monthly after one and two years.

Of over 1500 patients enrolled in study BM 16549 comparing monthly with daily dosing regimens of ibandronic acid, 14 % and 18 % of patients used histamine (H2) blockers or proton pump inhibitors after one and two years, respectively. Among these patients, the incidence of upper gastrointestinal events in the patients treated with Bonviva 150 mg once monthly was similar to that in patients treated with Bonviva 2.5 mg daily.

4.6 Pregnancy and lactation

There are no adequate data from the use of ibandronic acid in pregnant women. Studies in rats have shown some reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

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Bonviva should not be used during pregnancy.

It is not known whether ibandronic acid is excreted in human milk. Studies in lactating rats have demonstrated the presence of low levels of ibandronic acid in the milk following intravenous administration.

Bonviva should not be used during lactation.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

The safety of Bonviva 2.5 mg daily was evaluated in 1251 patients treated in 4 placebo-controlled clinical studies; 73 % of these patients came from the pivotal three-year treatment study (MF 4411). The overall safety profile of Bonviva 2.5 mg daily in all these studies was similar to that of placebo. The overall proportion of patients who experienced an adverse drug reaction, i.e. adverse event with a possible or probable relationship to trial medication, in the pivotal treatment study (MF 4411) was 19.8 % for Bonviva and 17.9 % for placebo.

In a two-year study in postmenopausal women with osteoporosis (BM 16549) the overall safety of Bonviva 150 mg once monthly and Bonviva 2.5 mg daily was similar. The overall proportion of patients who experienced an adverse drug reaction, i.e. adverse event with a possible or probable relationship to trial medication, was 22.7 % and 25.0 % for Bonviva 150 mg once monthly and 21.5 % and 22.5 % for Bonviva 2.5 mg daily after one and two years, respectively. The majority of adverse drug reactions were mild to moderate in intensity. Most cases did not lead to cessation of therapy.

Table 1 and table 2 list adverse drug reactions occurring in more than 1 % of patients treated with Bonviva 150 mg monthly or 2.5 mg daily in study BM 16549 and in patients treated with Bonviva 2.5 mg daily in study MF 4411. The tables show the adverse drug reactions in the two studies that occurred with a higher incidence than in patients treated with placebo in study MF 4411. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Data at one year from BM 16549 are represented in Table 1 and cumulative data for the two years from BM 16549 are represented in table 2.

Table 1: Common adverse drug reactions (>1/100, ≤ 1/10) in phase III osteoporosis studies that were considered by the investigator to be possibly or probably related to treatment - One year data from study BM 16549 and three year data from placebo-controlled fracture study MF 4411

	One year data in study BM 16549	Three year data in study MF 4411

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Act: 444 RESPUESTA REQUE Folios: 31

Señor
SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E. S. D.

Re: P1.-**F. HOFFMANN-LA ROCHE AG**-Solicitud de Patente de Invención en Fase Nacional PCT para "**ÁCIDO BISFOSFÓNICO PARA EL TRATAMIENTO Y PREVENCIÓN DE OSTEOPOROSIS**".-Clase **A61P 19/10**.-Expediente número **04-096.462.-**

1. Me refiero al auto dictado por ese Despacho notificado por fijación en lista el 14 de Marzo de 2008.

2. Con el fin de responder a las objeciones expuestas por el señor Examinador en su Concepto Técnico No. **422** bajo los acápites de Claridad de la solicitud y Reivindicaciones relativas a un uso o a un segundo uso, atentamente me permito presentar los siguientes argumentos técnicos y las siguientes modificaciones hechas en el capítulo reivindicatorio de la presente solicitud, mediante lo cual no sólo se superan dichas objeciones, sino que además se demuestra en forma contundente la patentabilidad de la presente solicitud.

3. **MODIFICACIONES A LA SOLICITUD**

Incialmente me permito manifestar que el solicitante de la invención en cuestión ha decidido presentar un nuevo capítulo reivindicatorio, el cual está compuesto por seis (6) reivindicaciones cuyo sustento se analiza a continuación:

- La nueva reivindicación 1 está dirigida a proteger un medicamento que comprende 100 mg ó 150 mg de un ácido bisfosfónico (o una sal

farmacéuticamente aceptable del mismo) junto con uno o más excipientes farmacéuticamente aceptables. Dicha nueva reivindicación presenta adecuado sustento en la páginas 6 (líneas 14 a 17) y 14 (líneas 1 a 6) de la memoria descriptiva originalmente presentada.

- La nueva reivindicación 2 define que el ácido bisfosfónico mencionado en la nueva reivindicación 1 es específicamente el ácido ibandrónico. Lo anterior presenta pleno sustento, por ejemplo, en la página 11 (líneas 17 a 20) de la descripción de la presente solicitud de patente.

- Las nuevas reivindicaciones 3 y 4 se encuentran dirigidas a proteger un medicamento de acuerdo con las reivindicaciones precedentes, el cual se caracteriza porque contiene específicamente 100 mg y 150 mg de ácido bisfosfónico (o una sal farmacéuticamente aceptable del mismo), respectivamente. En este caso, es claro que el sustento para dichas nuevas reivindicaciones es la nueva reivindicación 1, y por ende, la materia descrita en la página 6 (líneas 14 a 17) de la descripción.

- La nueva reivindicación 5 especifica que el ácido bisfosfónico (o la sal farmacéuticamente aceptable del mismo) mencionado en las reivindicaciones 1 a 4 precedentes es la sal monosódica del ácido ibandrónico monohidrato, de acuerdo a lo establecido en la página 13 (líneas 3 a 6) de la memoria descriptiva de la presente solicitud de patente).

- La nueva reivindicacion 6 está dirigida a proteger un medicamento de conformidad con lo descrito en las reivindicaciones 1 a 5 precedentes, el cual adicionalmente está caracterizado porque es un comprimido recubierto por una película, cuyo núcleo está conformado por 100 mg ó 150 mg de un ácido bisfosfónico (o una sal farmacéuticamente aceptable de este) y uno o más excipientes escogidos entre: lactosa, polivinilpirrolidona, celulosa microcristalina, crospovidona, ácido esteárico, dióxido de silicio, hidroxipropil metilcelulosa, óxido de titanio, talco y polietilenglicol 6000. Dicha nueva reivindicación presenta adecuado sustento en la página 14 (líneas 2 a 24) de la descripción originalmente presentada.

En vista de lo anterior, atentamente me permito resaltar que las modificaciones realizadas al capítulo reivindicatorio de la presente solicitud de patente **no amplían de manera alguna el alcance establecido en la memoria descriptiva originalmente presentada.** En este sentido, es claro que dichas modificaciones han sido realizadas con el único fin de cumplir con los requisitos de patentabilidad estipulados en la Decisión 486.

4. **CLARIDAD DE LA SOLICITUD**

El señor Examinador ha objetado la claridad de la presente solicitud con base en los siguientes argumentos:

DESCRIPCIÓN

> ***"No se encontraron datos comparativos con las composiciones previamente divulgadas que demuestren su aporte al estado de la técnica, y el efecto inesperado alcanzado"***

En respuesta a lo anterior, atentamente me permito poner en consideración del señor Examinador los siguientes documentos que permiten demostrar el sorprendente aporte al estado de la técnica brindado por la materia revelada en la presente solicitud de patente:

- **Epstein Solomon;** "Ibandronate Treatment for Osteoporosis: Rationale, Preclinical, and Clinical Development of Extended Dosing Regimens"; *Current Osteoporosis Reports; 2006; 4 (1); 14-20;* ***(Anexo A)***

- ***Once monthly dosing increases the proportion of patients who respond to oral ibandronate: 1-year results from MOBILE;*** *J. Bone Miner. Res.; Res 2004; 19 (Suppl. 1):S447 (Abstract M432);* ***(Anexo B)***

- **Monthly oral ibandronate significantly reduces bone resorption in postmenopausal osteoporosis: 1-year results from MOBILE;** J. Bone Miner. Res.; 2004; 19 (Suppl.1):S94 (Abstract F406); **(Anexo C)**

Con respecto al anexo A, considero de especial importancia resaltar los comentarios realizados por el autor de dicho documento en el tercer párrafo de las conclusiones (página 19); allí se establece que antes de los estudios experimentales que condujeron a obtener la sorprendente información revelada en la presente solicitud de patente, se asumía como parte del estado de la técnica que debido a que los osteoclastos tienen una vida media de entre 2 y 3 semanas, dicho rango era el máximo intervalo de tiempo que debía existir entre la administración de bisfosfonatos a un paciente en tratamiento. Sin embargo, en dicho documento se concluye que los estudios con ibandronato han demostrado que el intervalo de dosis puede ser extendido a un (1) mes sin que se vea alterada la eficacia del tratamiento.

Por su parte, con base en los estudios clínicos revelados en el anexo B, los autores de dicho documento concluyen que la gran mayoría de mujeres a las que se les administró mensualmente 100 mg o 150 mg de ibandronato lograron incrementos significativos en la densidad mineral ósea tanto en la espina lumbar (LS BMD), como en la cadera (HT BMD). Así, por ejemplo, de acuerdo a los datos revelados en la tabla 1 de dicho anexo B, es claro que un 91.3% de pacientes a las que se les administró mensualmente 150 mg de ibandronato mostraron un aumento en la densidad mineral ósea de la espina lumbar (LS BMD), mientras que sólo un 84% de pacientes a quienes se les administró diariamente 2.5 mg de ibandronato mostraron un aumento en LS BMD. Asimismo, un mayor porcentaje de pacientes a las que se les administró mensualmente 100 mg (87.1%) y 150 mg (90.0%) de ibandronato lograron aumentos substanciales en la densidad mineral ósea en la cadera (TH BMD), pues sólo un 76.7% de pacientes a las que se les administró diariamente 2.5 mg de ibandronato lograron incrementos similares en TH BMD.

Finalmente, en el anexo C básicamente se revela que la administración mensual de 150 mg de ibandronato a pacientes con osteoporosis postmenopáusica suprime marcadamente la magnitud de CTX en suero (enlaces de colágeno carboxi-terminal). Como consecuencia de lo anterior, la administración mensual de 150 mg de ibandronato suprime rápidamente la resorción ósea hasta niveles normales luego de tres meses de haber iniciado el tratamiento, con la característica adicional de que dicha supresión se mantiene mientras se mantenga el mismo esquema de administración del medicamento.

En síntesis, atentamente me permito resaltar ante ese Despacho que **los documentos previamente mencionados muestran claramente que el medicamento revelado en el nuevo capítulo reivindicatorio de la solicitud de patente en cuestión, esto es, una dosis única mensual de 100 mg ó 150 mg de ibandronato (o una sal farmacéuticamente aceptable del mismo), presenta marcadas ventajas terapéuticas frente a las composiciones previamente conocidas en el estado de la técnica, las cuales establecen terapias de dosificación de cantidades mas bajas de ibandronato administradas en intervalos de tiempo menores.**

En este sentido, puede concluirse que: 1) la eficacia terapéutica obtenida mediante las composiciones de la presente solicitud es tan o más alta que la obtenida con las dosificaciones enseñadas en el arte previo; y, 2) la aceptación por parte de las pacientes a un régimen de tratamiento mensual con ibandronato es mucho más alta con respecto a la aceptación dada a un régimen de tratamiento diario, semanal o quincenal, como consecuencia de las implicaciones que dichas formas de dosificación tienen en los efectos laterales negativos producidos por una administración recurrente de dicho compuesto activo.

5. REIVINDICACIONES RELATIVAS A UN USO O A UN SEGUNDO USO (artículos 14 y 21 D 486)

El señor Examinador afirma lo siguiente en su Concepto Técnico:

"Las reivindicaciones 1-10, se refieren al uso de los ácidos bisfosfónicos; las cuales no son patentables de acuerdo a los artículos mencionados de la normatividad vigente"

Atendiendo a la anterior objeción y tal como se comentó en el numeral 3 del presente memorial, el solicitante de la invención en cuestión ha decidido presentar un nuevo capítulo reivindicatorio, el cual está compuesto por seis (6) reivindicaciones dirigidas exclusivamente a proteger una composición (específicamente un medicamento). En este sentido, adicionalmente resulta de gran importancia resaltar que a lo largo del nuevo capítulo reivindicatorio dicha composición se encuentra adecuadamente caracterizada por sus componentes técnicos.

En vista de lo anterior, es claro que dicho nuevo capítulo reivindicatorio cumple a cabalidad con las disposiciones establecidas en el Artículo 30 de la Decisión 486, permitiendo de esta manera superar satisfactoriamente las objeciones realizadas por el señor Examinador a éste respecto.

6. ANÁLISIS DE LA NOVEDAD Y EL NIVEL INVENTIVO

De otro lado, si bien el señor Examinador aún no ha realizado el análisis de la novedad y el nivel inventivo del nuevo capítulo reivindicatorio de la presente solicitud de patente, en su Concepto Técnico de manera absolutamente **sorprendente** hace referencia a tres documentos citados por un supuesto "opositor", cuando es absolutamente evidente que el escrito de **"remisión de información"** presentado el 6 de Octubre de 2006 por parte del Dr. Reyes Villamizar, apoderado de Tecnoquímicas S.A., fue presentado **un año y cuatro meses después de expirado el término señalado por el artículo 42 de la Decisión 486,** para que cualquier tercero con legitimo interés presente oposiciones fundamentadas. Por lo tanto, es evidente que dicho escrito no puede de ninguna forma ser tenido en cuenta por este Despacho como un escrito de oposición, pues no sólo es extemporáneo, sino que nunca fue notificado a mi representada para dar respuesta al mismo, por **no** ser efectivamente una oposición.

Sin embargo, si aún ese Despacho considera que los tres documentos citados en el escrito de Tecnoquímicas pudieran llegar a afectar la patentabilidad de la presente invención, a continuación me permito presentar una serie de argumentos claros y contundentes que desvirtuan cualquier duda que pueda llegar a surgir acerca de la patentabilidad de la invención en estudio.

6.1 Consideraciones con respecto al documento D1

En términos generales, el documento **WO 0115703** enseña métodos terapéuticos diseñados para inhibir la resorción ósea en mamíferos, donde dichos métodos se caracterizan porque permiten minimizar los efectos gastrointestinales adversos que generan los métodos terapéuticos conocidos en el estado del arte.

Específicamente, dicho documento D1 revela un método para inhibir la resorción ósea en mamíferos, que comprende la administración oral de un bisfosfonato seleccionado entre alendronato, ibandronato, risedronato y las sales o ésteres farmacéuticamente aceptables de los mismos, dentro de un horario de administración seleccionado entre: dosis una vez por semana, dosis dos veces por semana, dosis cada dos semanas y dosis dos veces al mes.

Adicionalmente, en **D1** se enseña que una unidad de dosificación para inhibir la resorción ósea en mamíferos comprende entre aproximadamente 3.5 mg y aproximadamente 200 mg de ibandronato (incluyendo las sales o ésteres farmacéuticamente aceptables del mismo).

Ahora bien, con base en lo anterior y con el ánimo de demostrar el inequívoco carácter novedoso que presenta la materia revelada en el nuevo capítulo reivindicatorio de la presente solicitud de patente frente a las enseñanzas de D1, a continuación me permito presentar las siguientes consideraciones técnicas:

- Tal como se comentó previamente, en la reivindicación 4 del documento D1 se enseña una forma de dosificación que comprende entre aproximadamente 3.5 mg y aproximadamente 200 mg de ibandronato (o una de sus sales o ésteres farmacéuticamente aceptables).

  Contrario a esto, el nuevo capítulo reivindicatorio de la solicitud en cuestión está dirigido a proteger un medicamento que comprende 100 mg ó 150 mg de la sal monosódica del ácido ibandrónico monohidrato.

  De lo anterior queda claro que mientras D1 revela un rango de dosificación (3.5 mg a 200 mg), **en la presente solicitud de patente se protegen dos cantidades específicas de principio activo (100 mg y 150 mg)**, hecho que según las enseñanzas del Manual Andino, constituye un claro e inequívoco factor de novedad de la materia revelada en la solicitud de patente en cuestión (frente a las enseñanzas de D1), toda vez que de acuerdo con las disposiciones establecidas en el mencionado Manual: *"Una expresión general no*

destruye la novedad de un elemento específico que cae dentro de esta expresión".[1]

Adicionalmente, de la cuidadosa lectura de **D1** es claro que en dicha anterioridad no se revelan de manera explícita las cantidades específicas de ibandronato establecidas en la presente solicitud de patente, y debido a que en el Manual Andino de Patentes también se establece que: *"Para determinar la novedad de la invención, se debe comprobar si existen anticipaciones del estado de la técnica que contengan explícitamente todas las características técnicas esenciales de la invención. El examen de novedad se efectúa comparando elemento por elemento de la invención tal como está definido por las reivindicaciones con los del estado de la técnica"*,[2] es absolutamente claro que la materia definida en el nuevo capítulo reivindicatorio presenta un inobjetable carácter novedoso frente a las enseñanzas del documento D1.

- En conexión con lo anterior, resulta de gran importancia resaltar que tanto en algunos apartes de la descripción del documento **D1**, como en las reivindicaciones 7 a 10 de dicha anterioridad, se mencionan cantidades específicas de ibandronato (incluyendo sales ó ésteres del mismo), las cuales, sin embargo, no sólo no corresponden a las cantidades específicamente establecidas en la presente invención, sino que se encuentran marcadamente alejadas. En este sentido, mientras que en D1 se mencionan unidades de dosificación que comprenden 35 mg, 40 mg, 45 mg y 50 mg de ibandronato, la presente solicitud de patente está dirigda a proteger medicamentos que comprenden 100 mg ó 150 mg de ibandronato.

- De otro lado, a partir de una comparación básica entre el capítulo reivindicatorio del documento **D1** y el capítulo reivindicatorio de la presente invención, es claro que mientras la materia protegida en **D1** comprende exclusivamente métodos de tratamiento, el capítulo reivindicatorio que se remite junto con el presente memorial se

[1] SECRETARÍA GENERAL DE LA COMUNIDAD ANDINA. *Manual para el Examen de solicitudes de patentes de invención en las Oficinas de Propiedad Industrial de los Países de la Comunidad Andina.* Lima, Perú: 2004; Página: 67.
[2] Ibid, página: 65.

encuentra dirigido únicamente a proteger composiciones farmacéuticas.

En vista de lo anteriormente planteado, atentamente me permito manifestar que **la materia revelada en el nuevo capítulo reivindicatorio de la presente solicitud de patente presenta un inequívoco carácter novedoso con respecto a las enseñanzas del documento D1.**

De otro lado, a partir de la información analizada en el numeral 4 del presente memorial, en referencia a los sorprendentes beneficios mostrados por las composiciones farmacéuticas reveladas en la solicitud de patente en cuestión, así como a partir del cuidadoso análisis de la memoria descriptiva tanto del documento **D1** como de la presente solicitud de patente, es claro que el nuevo capítulo reivindicatorio que se remite junto con el presente memorial presenta un inobjetable carácter inventivo con respecto a las enseñanzas que conforman el estado de la técnica anterior. En este sentido, me permito resaltar las siguientes consideraciones técnicas:

- En primer lugar, el documento **D1** claramente establece un método para inhibir la resorción ósea en mamíferos, el cual comprende la administración oral de un bisfosfonato mediante un régimen seleccionado entre: dosis una vez por semana, dosis dos veces por semana, dosis cada dos semanas y dosis dos veces al mes.

  Sin embargo, **dicha anterioridad no revela y tampoco sugiere un medicamento que comprenda 100 mg ó 150 mg de ibandronato** (ó una sal farmacéuticamente aceptable del mismo) **y que sea administrado como una única dosis mensual**. Ahora, tal como se revela en los anexos A, B y C del presente memorial, dicha diferencia en el régimen de administración del medicamento permite la obtención de marcadas ventajas pues, por un lado, la eficacia terapéutica obtenida mediante las composiciones de la presente solicitud es tan o más alta que la obtenida con las dosificaciones enseñadas en el arte previo; y, por otro lado, la aceptación por parte de las pacientes a un régimen de tratamiento mensual con ibandronato es mucho más alta con respecto a la aceptación dada a un régimen de tratamiento diario, semanal o quincenal, como consecuencia de las implicaciones que dichas formas de dosificación

tienen en los efectos laterales negativos producidos por una administración recurrente de dicho compuesto activo.

- En conexión con lo anterior, resulta de gran importancia resaltar que el documento **D1** no sugiere de manera alguna la posible administración de bisfosfonatos en un régimen mensual, hecho que puede explicarse al tener en cuenta la información revelada en el artículo: *E. Solomon; Ibandronate Treatment for Osteoporosis: Rationale, Preclinical, and Clinical Development of Extended Dosing Regimens"; Current Osteoporosis Reports; 2006; 4 (1); 14-20,* en donde claramente se afirma que previo a la publicación de la presente solicitud de patente se asumía como parte del estado de la técnica que debido a que los osteoclastos tienen una vida media de entre 2 y 3 semanas, éste último rango era el máximo intervalo de tiempo que debía existir entre la administración de bisfosfonatos a un paciente en tratamiento.

En síntesis, atentamente me permito señalar que todo lo anteriormente planteado demuestra el inequívoco carácter novedoso e inventivo que presenta la materia revelada en la presente solicitud de patente con respecto a las enseñanzas del documento **D1**.

6.2 **Consideraciones con respecto al documento D2**

En el artículo científico *"Ibandronate: a comparison of oral daily doping versus intermittent doping in postmenopausal osteoporosis"* básicamente se revela un estudio clínico en el que se comparó la eficacia y seguridad de: 1) una dosificación oral intermitente de ibandronato y, 2) una dosificación oral contínua de ibandronato, en mujeres que padecen osteoporosis postmenopáusica.

De manera específica, en **D2** se revelan los resultados de un estudio clínico en el que se administró una dosis contínua diaria de 2.5 mg de ibandronato a un primer grupo de mujeres, y en el que paralelamente se administró a un segundo grupo de mujeres una dosis intermitente de 20 mg de ibandronato únicamente durante 24 días, seguido por 9 semanas sin la aplicación del medicamento.

Dicho estudio permitió concluir básicamente que los regímenes de administración contínua e intermitente de ibandronato en mujeres que padecen de osteoporosis postmenopáusica generan cambios equivalentes en la densidad mineral y en la renovación ósea.

Ahora bien, a partir de lo planteado previamente puede concluirse que **las enseñanzas del documento D2 tampoco afectan la novedad de la materia revelada en el nuevo capítulo revindicatorio de la presente solicitud de patente, toda vez que en dicha anterioridad de ninguna manera se revela un medicamento que comprenda 100 mg ó 150 mg de un bisfosfonato (o una sal farmacéuticamente aceptable del mismo), junto con excipientes farmacéuticamente aceptables.**

De conformidad con lo anterior, me permito resaltar una vez más que **D2** reporta únicamente un estudio clínico para el tratamiento de la osteoporosis, el cual de ninguna manera incluye la administración a las mujeres que hicieron parte de dicho estudio clínico de un medicamento que comprenda un bisfosfonato en las cantidades definidas dentro de la presente solicitud de patente, esto es, 100 mg ó 150 mg de dicho compuesto activo.

De otro lado, con respecto al salto inventivo logrado en el estado de la técnica por cuenta de la materia revelada en la presente solicitud de patente, con respecto a las enseñanzas del documento D2, resulta de gran importancia tener en cuenta las siguientes consideraciones:

- Por un lado, dicha anterioridad enseña únicamente terapias de tratamiento que incluyen la administración de: 1) dosis diarias de 2.5 mg de ibandronato, ó 2) dosis intermitentes de 20 mg de ibandronato únicamente durante 24 días, seguidos por 9 semanas sin la aplicación del medicamento.

  Sin embargo, **dicha anterioridad no revela y tampoco sugiere un medicamento que comprenda 100 mg ó 150 mg de ibandronato** (ó una sal farmacéuticamente aceptable del mismo) **y que sea administrado como una única dosis mensual.** Ahora, tal como se ha comentado previamente en el presente memorial, dichas modificaciones tanto en la cantidad de dosis de bisfosfonatos, como

en el régimen de administración, implica la obtención de sorprendentes ventajas terapéuticas, las cuales de ninguna manera habrían podido ser sugeridas por una persona versada en la materia en cuestión, puesto que antes de los estudios experimentales que condujeron a obtener la información revelada en la presente solicitud de patente se asumía como parte del estado de la técnica que debido a que los osteoclastos tienen una vida media de entre 2 y 3 semanas, éste último rango era el máximo intervalo de tiempo que debía existir entre la administración de bisfosfonatos a un paciente en tratamiento (Ver anexo B).

- Aparte de lo anterior, resulta de gran importancia resaltar que las características técnicas del novedoso medicamento revelado en la presente solicitud de patente tampoco pueden considerarse obvias y/o lógicas por una persona experta en la materia si se tiene en cuenta que una composición farmacéutica que comprenda 100 mg ó 150 mg de ibandronato para administración mensual, ni siquiera corresponde a la simple suma de las treinta dosis diarias de ibandronato sugeridas en el estado de la técnica. En este sentido, por ejemplo, según las enseñanzas de **D2** la dosis diaria corresponde a 2.5 mg, lo cual significa que un paciente tratado bajo ese régimen de administración consumiría tan sólo 75 mg mensuales de ibandronato. Como puede notarse, las características técnicas del medicamento revelado en la presente solicitud de patente implican la administración de el 120% ó el 200% de la dosis de ibandronato sugerida por el estado de la técnica. Sin embargo, sorprendentemente se ha encontrado que dichas dosis ofrecen mayores ventajas para el paciente, tanto en una notable reducción en fracturas, como en comodidad y aceptación.

En vista de lo planteado previamente, atentamente me permito manifestar que las enseñanzas del documento D2 tampoco afectan la novedad y el nivel inventivo de la materia revelada en el nuevo capítulo reivindicatorio de la presente solicitud de patente.

6.3 **Consideraciones con respecto al documento D3**

En términos generales, el documento **WO 9739755** enseña composiciones farmacéuticas para aplicación oral que contienen ibandronato o una sal fisiológicamente tolerable del mismo.

De acuerdo a los autores de dicho documento cada forma de administración de dichas composiciones consiste de una sección interior que contiene el ingrediente activo, la cual está rodeada por un revestimiento libre de ingrediente activo, lo cual permite que éste último sea liberado rápidamente.

Ahora bien, de lo anterior es claro que dicho documento D3 únicamente se limita a enseñar de manera general composiciones de ácido ibandrónico para administración oral. Por lo tanto, es claro que tal anterioridad NO indica de manera alguna la cantidad de ibandronato contenida en la sección interior de dichas composiciones farmacéuticas.

Con base en lo anterior, es decir, debido a que en **D3** de ninguna manera se revela un medicamento que comprenda 100 mg ó 150 mg de un bisfosfonato (o una sal farmacéuticamente aceptable del mismo), junto con excipientes farmacéuticamente aceptables, es claro que la materia revelada en el nuevo capítulo reivindicatorio de la solicitud de patente en cuestión presenta un inobjetable carácter novedoso frente a las enseñanzas del documento D3.

Aparte de lo anterior, del atento análisis de la información revelada en el documento **D3** es posible concluir adicionalmente que dicha anterioridad no afecta de manera alguna el carácter inventivo de la materia revelada en la presente solicitud de patente, toda vez que una persona experta en la materia técnica en cuestión no encuentra en **D3** enseñanza alguna que le sugiera un medicamento de administración mensual que comprenda 100 ó 150 mg de ibandronato (o una sal farmacéuticamente aceptable del mismo) junto con excipientes farmacéuticamente aceptables. Asimismo, es claro que la persona experta en la materia tampoco encontraría obvio el medicamento de la solicitud de patente en cuestión, debido a que éste no habría podido sugerir las notables ventajas técnicas y terapéuticas obtenidas a partir de dicha novedosa composición, tal como se ha comentado previamente en el presente memorial.

7. CONCLUSIÓN

En virtud de todo lo anterior, atentamente me permito señalar ante ese Despacho que de conformidad con las drásticas modificaciones realizadas en el capítulo reivindicatorio de la presente solicitud de patente, así como con base en la información y los argumentos técnicos presentados para demostrar el inequívoco carácter novedoso y el sorprendente aporte al estado de la técnica brindado por la materia revelada en dicha solicitud, es completamente claro que se han superado las objeciones expuestas por el señor Examinador, y por lo tanto, dicha solicitud es merecedora del privilegio de patente solicitado.

8. Anexo al presente memorial me permito presentar:

(a) Recibo número 08-44,778, expedido por la Superintendencia de Industria y Comercio, que acredita el pago de las modificaciones mencionadas;

(b) Copia del nuevo capítulo reivindicatorio compuesto por seis (6) reivindicaciones, que reemplaza al Capítulo Reivindicatorio originalmente presentado y en el cual se han realizado las modificaciones anteriormente mencionadas;

(c) Anexo A: E. Solomon; "Ibandronate Treatment for Osteoporosis: Rationale, Preclinical, and Clinical Development of Extended Dosing Regimens"; *Current Osteoporosis Reports; 2006; 4 (1); 14-20;*

(d) *Anexo B: Once monthly dosing increases the proportion of patients who respond to oral ibandronate: 1-year results from MOBILE; J. Bone Miner. Res.; Res 2004; 19 (Suppl. 1):S447 (Abstract M432); y*

(e) Anexo C: Monthly oral ibandronate significantly reduces bone resorption in postmenopausal osteoporosis: 1-year results from MOBILE; J. Bone Miner. Res.; 2004; 19 (Suppl.1):S94 (Abstract F406);

9. En vista de lo anterior, ruego a usted proceder a estudiar nuevamente la solicitud a la luz de las argumentaciones presentadas y conceder el privilegio de patente solicitado.

Señor Superintendente,

ALICIA LLOREDA RICAURTE

T.P. 53.215

Lloreda Alicia Ricaurte

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C.C. No. 39.690.713 de Usaquén

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 44,778
FECHA : JUNIO 5 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 04-096462- -00005-0000

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Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 444 RESPUESTARLQUE Folios: 31

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
LLOREDA Y CIA S. A	CONSIGNACION	BANCO DE BOGOTA	062754387	2756091	05/06/2008	6,040,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-03 CAMBIO DE MODALIDAD Y MODIFICA	12 MARCAS Y LEMAS COMERCIALES	103,000.00
		TOTAL : $	103,000.00

SON: CIENTO TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

REIVINDICACIONES

1. Un medicamento administrado mensualmente de manera oral, caracterizado porque comprende 100 mg ó 150 mg de un ácido bisfosfónico o una sal farmacéuticamente aceptable del mismo, y uno o más excipientes farmacéuticamente aceptables.

2. El medicamento de la reivindicación 1, en donde el ácido bisfosfónico es el ácido ibandrónico o una sal farmacéuticamente aceptable del mismo.

3. El medicamento de las reivindicaciones 1 y 2, el cual comprende 100 mg de ácido bisfosfónico o una sal farmacéuticamente aceptable del mismo.

4. El medicamento de las reivindicaciones 1 y 2, el cual comprende 150 mg de ácido bisfosfónico o una sal farmacéuticamente aceptable del mismo.

5. El medicamento de acuerdo con cualquiera de las reivindicaciones 1 a 4, en donde el ácido bisfosfónico o la sal farmacéuticamente aceptable del mismo es la sal monosódica del ácido ibandrónico, monohidrato.

6. El medicamento de acuerdo con cualquiera de las reivindicaciones 1 a 5, caracterizado porque es un comprimido recubierto por una película, y en donde el núcleo del comprimido comprende:

- 100 mg o 150 mg de un ácido bisfosfónico o una sal farmacéuticamente aceptable del mismo, de acuerdo con cualquiera de las reivindicaciones 1 a 5;

- Uno o más excipientes farmacéuticamente aceptables seleccionados del grupo conformado por: lactosa, polivinilpirrolidona, celulosa microcristalina, crospovidona, ácido esteárico y dióxido de silicio; y,

- Uno o más excipientes farmacéuticamente aceptables seleccionados del grupo conformado por: hidroxipropil metilcelulosa, óxido de titanio, talco y polietilenglicol 6000.

Ibandronate Treatment for Osteoporosis: Rationale, Preclinical, and Clinical Development of Extended Dosing Regimens

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Ibandronate is a potent nitrogen-containing bisphosphonate available as a once-monthly oral formulation for the treatment and prevention of osteoporosis. Preclinical experiments with estrogen-depleted rats, dogs, and monkeys demonstrated the efficacy of daily and intermittent ibandronate dosing. Initial clinical trials explored the optimal dosing regimens for oral administration in humans. The Oral Ibandronate Osteoporosis Vertebral Fracture Trial in North America and Europe (BONE) and Monthly Oral Ibandronate in Ladies (MOBILE) trials demonstrated that long-term daily and intermittent administration of ibandronate was efficacious for increasing bone mineral density, reducing markers of bone turnover, and preventing fractures, while maintaining bone quality. These preclinical and clinical ibandronate trials provided progressive evidence that a simple, long interval dosing regimen could offer efficacy and safety comparable with currently available bisphosphonates. It is anticipated that once-monthly ibandronate may have a positive impact on patient adherence, and ultimately, on fracture protection in osteoporotic women.

Introduction

Bone mass is maintained as part of a balance between bone formation and resorption. In patients with postmenopausal osteoporosis (PMO), resorption exceeds formation, resulting in reduced bone mass and a deterioration of bone microarchitecture. Bisphosphonates, at clinically relevant doses, have been shown to reduce the rate of bone loss, increase bone mineral density (BMD), and reduce fracture risk [1].

The chemical structure of bisphosphonates is similar to that of inorganic pyrophosphate; however, bisphosphonates have a phosphorous-carbon-phosphorous backbone. Their high affinity for bone is due to a hydroxyl group at the R^1 position that binds to Ca^{2+} ions in hydroxyapatite bone mineral surfaces at sites of osteoclast activity [2]. The antiresorptive potency of individual bisphosphonates is determined by their R^2 side chain constituents [3].

Radio-labeled molecules were used to demonstrate that bisphosphonates are internalized by osteoclasts [4,5]. Once inside the osteoclasts, bisphosphonates containing nitrogen in the moiety at the R^2 position inhibit osteoclast function predominantly through inhibition of farnesyl pyrophosphate (FPP) synthase, an enzyme of the mevalonate pathway [2]. Inhibition of FPP synthase prevents prenylation of small GTPases such as members of the Ras, Rho, Rab, Rac, and Cdc42 subfamilies [2]. This, in turn, disrupts a variety of cell processes important for osteoclast function, including cytoskeletal rearrangement, membrane ruffling, and intracellular vesicle trafficking, resulting in osteoclast apoptosis [2,6]. Osteoclast apoptosis is not necessary for inhibition of bone resorption [7•]. Bisphosphonates also affect bone formation, mainly through reduction of activation frequency, as evidenced by a reduction in bone formation surfaces [8–10], but this occurs to a lesser extent than resorption [1]. The net result of bisphosphonate administration is a gain in BMD.

The duration of bisphosphonate action is dependent on a combination of factors, notably potency, dose, dosing interval, and bone turnover rate [11••]. It has been proposed that differences in the degree to which a bisphosphonate binds to bone are responsible for the varying persistence of its skeletal actions, affecting potency and duration of action [11••,12]. However, this may not be the case and the potency of inhibition of the FPP synthase system is considered to be a predominant

factor [2,13]. To facilitate intermittent dosing, a bisphosphonate must be biologically active in sufficient quantity to inhibit bone turnover for the entire between-dose interval and potent enough to maintain dosing within a range that is well tolerated but still effective [14].

Ibandronate is a highly potent, nitrogen-containing bisphosphonate. The tertiary nitrogen group in the R^2 side chain position, coupled with the hydroxyl group in its R^1 lateral chain, renders ibandronate approximately two-fold, 10-fold, 50-fold, and 500-fold more potent than risedronate, alendronate, pamidronate, and clodronate, respectively, as measured by bone resorption inhibitory activity in the arotinoid assay in rats [15]. As mentioned previously, potency is an important factor in the development of simplified dosing regimens with extended between-dose intervals. In this paper the preclinical evidence for extended dosing along with recently published clinical trial data in which the therapeutic advantages of ibandronate, hypothesized during the drug development process will be reviewed.

Preclinical Data

The World Health Organization has acknowledged the value of preclinical studies in the development of osteoporosis drugs [16]. Currently available bisphosphonates, notably alendronate, risedronate, and zoledronate, have been extensively tested in animal models [8,17–25]. In ovariectomized rats and nonhuman primates, these agents were shown to prevent bone turnover, while increasing BMD [8,17–21]. Studies in dogs have been used to examine micro-damage accumulation and have shown that long-term administration with pharmacologic doses of these compounds does not negatively affect bone quality [22–25].

Ibandronate efficacy has been demonstrated in four animal models, rat, dog, monkey, and mini-pig (not included in this review). Food and Drug Administration (FDA) guidelines recommend that agents for the prevention or treatment of osteoporosis be tested in two different species, the ovariectomized rat and a second non-rat model [26]. Ovariectomized rats are utilized because the bone loss observed in this animal model is similar to that experienced by postmenopausal women [27]. In both groups, there is an increase in bone turnover rate, with an initial phase of rapid bone loss followed-up by a period with a marked decrease, a higher degree of loss of cancellous versus cortical bone, and a decrease in calcium absorption [27]. Both rats and humans respond to treatment with estrogen therapy, tamoxifen, bisphosphonates, parathyroid hormone, calcitonin, vitamin D, and exercise [27]. The main difference between the two species is that rats do not undergo menopause during mid-life followed-up by a period of accelerated bone loss [27]. In addition, aged ovariectomized rats 8 months or older are a more appropriate model of PMO than younger, actively growing rats. By using older rats, ibandronate studies eliminated potential confounding factors, including bones that are still actively growing and age-dependent metabolic activities [28•].

In an initial dose-ranging study, 8-month old ovariectomized or sham-operated rats were treated immediately after surgery with daily ibandronate in doses from 0.1 to 30.0 μg/kg or vehicle. Ibandronate dose-dependently inhibited bone loss, as measured by changes in the radiographic density of the proximal metaphyses of the tibias [28•]. The optimal dose (the lowest dose that was not significantly different from the sham-operated solvent control) was 1 μg/kg/d [28•]. Administering a loading dose to attain an immediate steady-state level of drug, did not affect the results [28•].

In an extension of the study described above, varying treatment regimens were administered over a period of 20 to 22 weeks, such that the total cumulative dose per ovariectomized animal equaled 154 μg/kg [28•]. The between-treatment intervals were derived by taking into account the bone remodeling time in rats and findings that the effects of a single dose of ibandronate lasted 2 to 3 weeks in a model of retinoid-stimulated bone destruction [15]. The therapy-free intervals were chosen to be one, two, or three times the length of the bone turnover cycle in rats [28•]. Animals received 1 week "on" treatment, followed-up by a therapy-free interval of 2, 4, or 6 weeks [28•]. After completing the required number of cycles, the rats received an additional week "on" treatment. The radiographic densities of femurs from all groups of treated animals remained equivalent to those of sham-operated controls [28•]. This pivotal study demonstrated that the interval between doses could exceed estimated bone turnover time while maintaining efficacy.

In a follow-up study, 8-month old ovariectomized or sham-operated rats were treated, 10 weeks after surgery, with daily subcutaneous ibandronate (0.2 to 25 μg/kg) or intermittent ibandronate (25 or 125 μg/kg every 25 days) for 12 months [29]. The 10-week post-surgery interval allowed for substantial bone loss to accumulate prior to treatment. Concentrations of ibandronate in bone were linear with respect to dose, suggesting linear kinetics within the range administered. The skeletal uptake of ibandronate was related to total dose, regardless of administration schedule. Dose-dependent increases were seen in BMD, trabecular bone volume and trabecular number, load to failure, and yield loads in long bones and vertebrae [29].

As part of a long-term safety study, 6-week old female and male Wistar rats were given vehicle or 3, 7, or 15 mg/kg/d of ibandronate orally by gavage for 104 weeks. Compressive strength, BMD, and stiffness were significantly higher in ibandronate-treated versus vehicle-treated rats [30]. The doses of ibandronate given to the rats in this study far exceeded doses given in earlier studies to simulate long-term therapy. Lifelong administration of ibandronate increased BMD and maintained or improved bone quality [30].

Concerns have been discussed relating to long-term administration of bisphosphonates and the theoretic possibility the chronic reductions in bone turnover may result in accumulation of micro-fractures, normally repaired by bone remodeling, which could cause bone fatigue fractures [31]. Evidence supporting this concept was reported in a study involving long-term administration of etidronate in dogs [10]. In contrast, the ibandronate safety study in rats found significant increases in ultimate load and stress values with long-term ibandronate treatment [30]. The results indicate that micro-fracture accumulation and reduced compressive strength of vertebral bodies did not occur in the rat preclinical trials [30].

In addition to rats, dose-response osteoporosis prevention studies with ibandronate were performed in dogs. Ovariohysterectomized (OHX) dogs were injected subcutaneously with vehicle or ibandronate doses ranging from 0.1 to 100 μg/kg/d for 1 month [32]. The dogs given vehicle exhibited a significant decrease in bone volume within 1 month of OHX surgery [32]. Ibandronate, in doses of greater than or equal to 1 μg/kg/d, was required to prevent bone loss [32]. No adverse effects on bone structure, formation, or resorption were seen in sham-operated dogs receiving ibandronate at doses of 1 μg/kg/d [32].

In a second study that examined osteoporosis treatment in dogs, ibandronate was administered daily and intermittently for 1 year to OHX dogs 4 months after surgery (to allow for development of bone loss) [33]. Dogs on the intermittent ibandronate dosing regimen received the same cumulative dose as dogs receiving the highest continuous daily dose (3640 μg/kg/d) [33]. Dogs were monitored for 12 months after initiation of treatment. Ibandronate (14 μg/kg/d or intermittently dosed) completely reversed bone loss, as measured by bone volume, to levels similar to baseline values [33]. Intermittent dosing in this study did not significantly reduce or suppress bone turnover as determined by histomorphometry and bone mineral properties as measured by Fourier-transform infrared macrospectroscopy [33]. It was theorized that the 65 μg/kg/d intermittent dose would be sufficiently potent to suppress bone resorption while allowing more bone to form during the treatment-free periods [33].

In a study using a dog model developed to simulate fracture repair, 24-month old dogs received daily ibandronate, intermittent dosing of ibandronate with 2- to 6-week, dose-free intervals, or vehicle for 36 weeks [34]. Animals in the active dosing regimens all received the same total dose of ibandronate over the entire treatment period (252 μg/kg over 36 weeks) [34]. In week 27 or 28, tiny holes were drilled in the left tibia, and a bone marrow ablation was performed on the ipsilateral femur [34]. Ibandronate administration did not quantitatively or qualitatively affect the initial stage of bone repair healing and it did not affect the activation of cortical remodeling that occurs during the second stage of fracture healing [34].

Ibandronate was tested further in non-human primates, which are the most similar to humans as they have similar reproductive hormone patterns and menstrual cycles. Ovariectomized monkeys are considered the best model for studying the efficacy of anti-osteoporotic drugs [16]. After ovariectomies, cynomolgus monkeys exhibit changes in bone mass and turnover similar to what is observed in postmenopausal women [35,36].

In dose-ranging osteoporosis prevention studies in monkeys, 66 ovariectomized or sham-operated monkeys were given intravenous bolus injections of placebo or 10, 30, or 150 μg/kg of ibandronate at 30-day intervals for 16 months [16,37,38]. Doses were chosen based on the rat and dog studies and were meant to represent a suboptimal dose, the optimal effective dose, and five times the optimal dose [38]. Suboptimal dosing (10 μg/kg) of ibandronate only partially prevented OVX-induced effects [37]. Thirty μg/kg of ibandronate prevented osteopenia, while 150 μg/kg of ibandronate increased bone mass (measured by dual-energy x-ray absorptiometry [DXA] bone densitometry) and improved bone strength at the spine and femoral neck (measured by biomechanical testing of lumbar vertebrae—compression, whole ulnae in 3-point bending, and femoral neck strength), without having a negative effect on bone quality [37].

This was the first non-human primate study to use a bisphosphonate dosing schedule resembling a clinical regimen [11••,37]. Consequently, clinical trials with bolus intravenous administration of ibandronate every 3 months were initiated [39]. Data from monkeys were consistent with results obtained in phase II clinical trials [37–39]. Intravenous bolus injections of ibandronate every 3 months increased lumbar spine BMD by 5.2% after 12 months in postmenopausal women (2 mg) and approximately 4% in monkeys (eight monthly doses of 150 μg/kg/dose) [37,39].

Overall, the results from animal studies indicated that oral gavage, subcutaneous, or intravenous administration of ibandronate with extended dosing intervals reduced bone turnover, increased BMD, and maintained bone quality. Findings with all three species were consistent—ibandronate had a dose-dependent effect on BMD in estrogen-depleted animals. The optimal dose of ibandronate in rats, dogs, and monkeys was 1 μg/kg/d administered subcutaneously [28•,32,33,37].

Preclinical studies also demonstrated that bone quality was maintained with long-term administration of ibandronate, [30,33,34,37] a finding that is necessary for long-term safety. In rats receiving ibandronate for 104 weeks, bone quality was maintained or improved [30]. In both studies of OHX dogs receiving daily or intermittent ibandronate for 1 year and ovariectomized monkeys treated with monthly injections of ibandronate for 16 months, histomorphometric analyses demonstrated that bone structure remained normal [33,37]. The demonstrated efficacy of ibandronate for the prevention and

treatment of osteoporosis in animal models, coupled with maintenance of bone quality, provided the basis for the development of intermittent dosing regimens in clinical trials.

Phase I and II Studies

Phase I and II trials were aimed at determining the optimal dose and dosing frequency. Based on initial tests in rats comparing ibandronate with other bisphosphonates, the predicted active dose of ibandronate in humans was estimated to be approximately 0.8 to 1.0 mg/day [15].

The estimated range was expanded, and a placebo-controlled, dose-finding study was performed in which women received ibandronate in doses from 0.25 to 5.0 mg/d for 12 months [40]. Ibandronate 2.5 mg/d was determined to be the most effective dose (similar treatment effects were observed in patients receiving 5.0 mg/d) [40]. Oral daily ibandronate reduced bone turnover markers, increased total body bone mineral content, and significantly increased BMD at the lumbar spine, total proximal femur, trochanter, and femoral neck [40].

Similar results were seen in a separate study in which daily dosing was compared with intermittent dosing (2.5 mg of oral ibandronate daily or 20 mg oral ibandronate every other day for the first 24 days out of every 3 months) [41]. Significant reductions in bone markers of resorption and formation were observed and maintained throughout the study [41]. Daily and intermittent dosing led to similar numeric increases in BMD at the lumbar spine, total hip, trochanter, and femoral neck after 2 years [41].

A review of three ibandronate phase II studies noted that the efficacy achieved with ibandronate was similar regardless of treatment regimen, whether administered orally 2.5 mg daily, orally 20 mg every other day for 12 doses every 3 months, or intravenously once every 3 months [42]. There were comparable increases in BMD and significant reductions in biochemical markers of bone turnover with all three regimens tested [39–41].

Findings in phase I and II clinical trials served as the basis for the development of phase III studies such as the Oral Ibandronate Osteoporosis Vertebral Fracture Trial in North America and Europe (BONE) and the Monthly Oral Ibandronate in Ladies (MOBILE) trials, which evaluated daily and intermittent dosing ibandronate regimens in postmenopausal women.

BONE Study

The BONE trial was a 3-year, randomized, double-blind, placebo-controlled, parallel-group study, and the only ibandronate trial to date with a fracture endpoint. Postmenopausal women (n = 2946) with a BMD T-score of -2.0 to -5.0 in at least one vertebra (L1-L4) and one to four prevalent vertebral fractures (T4-L4) received placebo or oral ibandronate 2.5 mg daily or 20 mg every other day for 12 doses every 3 months [43•]. The primary endpoint of the study was the rate of new morphometric fractures with 3 years of treatment. Secondary measures included the rate of new or worsening vertebral fractures, clinical vertebral fractures, and clinical osteoporotic nonvertebral fractures, BMD changes at the lumbar spine and proximal femur, changes in levels of bone resorption and formation markers, and changes in height [43•].

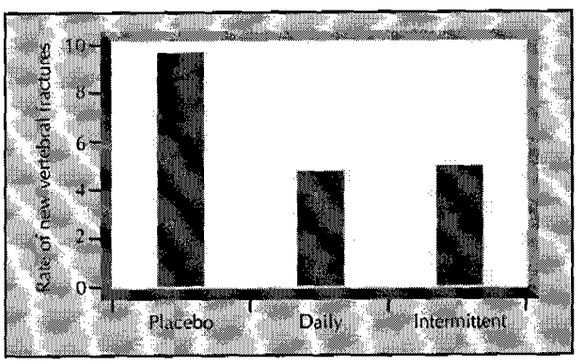


Figure 1. BONE study: incidence of new vertebral fractures after 3 years for patients dosed with daily and intermittent ibandronate and placebo.

Rate of new vertebral fractures was reduced in patients taking daily ibandronate (4.7%) and intermittent ibandronate (4.9%), compared with placebo (9.6%) (Fig. 1) [43•]. This corresponds to a reduction in the risk for new vertebral fractures of 52% (P = 0.0001) and 50% (P = 0.0006) for daily and intermittent dosing, respectively [43•]. Reductions in the incidence rates of new clinical vertebral fractures were 2.8% for daily and intermittent ibandronate dosing, compared with 5.3% for the placebo group [43•]; relative risk reduction of 49% for daily dosing, and 48% for intermittent dosing [43•]. In a post hoc analysis, it was determined that in higher-risk patients (baseline femoral neck BMD T-score of < -3.0), there was a reduction in the relative risk for nonvertebral fractures of 69% (P = 0.013) and 37% (P = 0.22) for daily and intermittent dosing, respectively. Significantly more height loss was observed in patients receiving placebo (5.6 mm) versus 3.9 mm (P = 0.0005) for daily and 4.7 mm (P = 0.0144) for intermittent dosing. Increases in lumbar spine BMD of 6.5%, 5.7%, and 1.3% were observed for daily, intermittent dosing, and placebo, respectively [43•]. Total hip BMD increased by 3.4% and 2.9% in the daily and intermittent dosing groups, respectively, while there was a net loss of 0.7% in the placebo group [43•]. Femoral neck BMD was increased by 2.8% and 2.4% in the daily and intermittent dosing groups, respectively, with a net loss of 0.6% in the placebo group [43•]. Trochanter BMD increased by 5.5%, 5.2%, and 0.2% in the daily, intermittent, and placebo groups, respectively [43•].

Within 3 months and throughout the 3-year study, there were significant reductions in bone resorption and

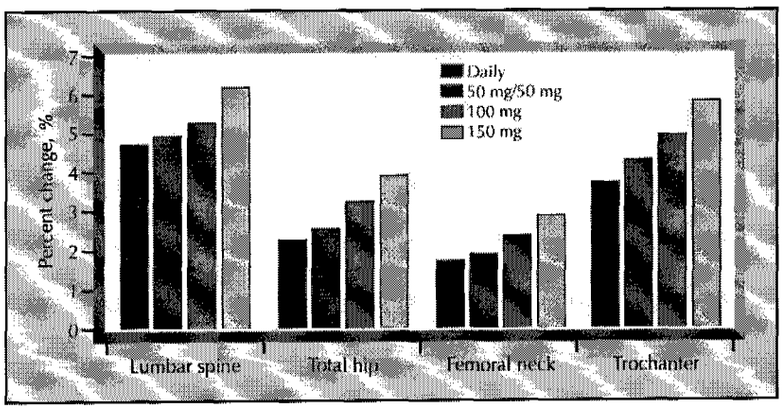


Figure 2. MOBILE study: changes from baseline in lumbar spine bone mineral density for patients treated with daily and intermittent ibandronate at 2 years.

formation markers in patients on both ibandronate treatment regimens versus placebo. C-telopeptide of type I collagen (CTX)/creatinine and N-telopeptide of type I collagen (NTX)/creatinine were reduced by 65.3% and 68.3% in the daily dosing group and 52.7% and 59.2% in the intermittent dosing group ($P < 0.001$ for both groups vs the placebo group) [44]. Levels of osteocalcin were reduced by 35.8% in the daily dosing group and 40.9% in the intermittent dosing group versus 2.1% in the placebo group ($P < 0.001$ for both ibandronate groups) [44].

A histomorphometric evaluation of a subgroup of patients from the BONE study assessed bone quality and architecture [45]. Patients underwent a transiliac bone biopsy at month 22 or 34 of treatment. In all cases, newly formed trabecular bone retained its structure with no indications of woven bone, marrow fibrosis, or signs of cellular toxicity [45]. A qualitative assessment found no impairment in bone matrix mineralization [45].

The BONE clinical trial demonstrated for the first time that significant fracture efficacy could be achieved with an intermittently administered bisphosphonate. While the study demonstrated that intermittent dosing was possible, the dosing regimen used in the study was not practical. The MOBILE study was initiated to examine efficacy with a more simplified dosing regimen (once monthly).

MOBILE Study

The MOBILE trial was a 2-year, randomized, double-blind, parallel-group, noninferiority, phase III ibandronate study and was the first bisphosphonate trial to evaluate a monthly oral regimen. Postmenopausal women ($n = 1609$) 55 to 80 years of age with osteoporosis (mean lumbar spine [L2-L4] BMD T-scores of -2.5 to -5.0) were included. Baseline assessments for the presence of vertebral fractures were not performed in this trial.

Upon enrollment, participants were randomized to one of four ibandronate treatment groups—2.5 mg daily, 50+50 mg once-monthly (50-mg dose given for 2 consecutive days), 100 mg once-monthly, and 150 mg once-monthly. Results from this study were analyzed after 1 and 2 years. The primary efficacy endpoint was the percent increase from baseline in lumbar spine BMD, as measured by DXA after 1 year. Secondary endpoints included measurements of BMD of the lumbar spine and proximal femur (total hip, femoral neck, trochanter) at 2 years. This information was used to assess the proportion of patients achieving predefined increases in the lumbar spine and total hip; measurements that have previously been identified as being associated with antifracture efficacy [46,47]. Changes from baseline in serum CTX (sCTX) concentrations were also measured at 3, 6, 12, and 24 months.

After 1 year, lumber spine BMD increased in the daily and monthly dosing groups [48•]. Noninferiority was established, given that the lower boundary of each one-sided 97.5% confidence interval was above the predetermined noninferiority margin for each comparison of a monthly versus the daily dose [48•]. Having demonstrated noninferiority, further testing was performed, which confirmed that the monthly dosing regimens and the 150-mg dose in particular, were superior to daily dosing [48•]. Lumbar spine BMD measurements increased in all treatment groups after 1 year. Numerically greater increases were seen in the once-monthly treatment groups compared with the daily dosing group. The largest increase was seen in patients receiving 150 mg of ibandronate monthly (4.9% vs 3.9% for daily dosing) [48•]. Increases in BMD were also seen in the proximal femur (total hip, femoral neck, trochanter) measurements, with the largest increases seen in the 150-mg dosing group [48•]. Decreases in sCTX were comparable in the daily and once-monthly dosing groups, 67.3% and 75.8% in the daily 2.5- and 150-mg monthly arms, respectively [48•].

Preliminary analyses of data after 2 years confirm the conclusions drawn from the first year's data—monthly ibandronate dosing is at least as effective as daily dosing for the treatment of osteoporosis [48•]. Increases in lumbar spine BMD were observed in the 150-mg once-monthly and daily treatment groups (6.6% and 5.0%, respectively) (Fig. 2) (Reginster, Unpublished data). This represented an increase in BMD from the first year results. Increases in proximal femur BMD (total hip, 4.2% and

2.5%; femoral neck, 3.1% and 1.9%; and trochanter, 6.2% and 4.0% for once-monthly and once-daily, respectively) were also observed. The decreases in sCTX, which were observed after 3 months, were maintained.

Conclusions

The development of extended dosing regimens for ibandronate was achieved through studies progressing from nonprimates, to nonhuman primates, to humans. Animal studies established that it was the cumulative dose of ibandronate, irrespective of dosing regimen, which was related to treatment effectiveness. These studies also demonstrated that bone quality was not compromised with long-term administration. The optimal subcutaneous dose of ibandronate, as determined in animal studies, was the equivalent of 1 μg/kg/d. Adjustments in dosing were made in human studies, which utilized oral administration, to account for the drug's low oral bio-availability.

Phase I and II studies determined the appropriate oral dosing levels and demonstrated the efficacy of ibandronate when administered using various intermittent dosing schedules in humans. Phase III trials, such as BONE and MOBILE, confirmed the long-term efficacy of ibandronate in humans with respect to multiple endpoints, including BMD, bone turnover markers, fracture rates, and bone quality. In the MOBILE study, the optimal dosage for once-monthly administration was determined. Ibandronate (150 mg) is currently the only bisphosphonate approved by the FDA for once-monthly oral dosing for the treatment and prevention of osteoporosis. Ibandronate is the first medication approved for monthly dosing of a chronic condition.

It remains a point of interest to determine the limits of the length of the between-dose interval. Since osteoclasts have a half-life of 2 to 3 weeks, this was believed to be the longest interval possible between bisphosphonate dosing. Studies with ibandronate have demonstrated that the dosing interval can be extended to once-monthly and beyond with maintenance of efficacy. It has been hypothesized that ibandronate released when the bone surface it is deposited on is resorbed may still be pharmacologically active. The limits of the administered doses and between-dose intervals have yet to be determined.

Results from a crossover trial evaluating patient preferences for once-weekly alendronate versus once-monthly ibandronate demonstrated that the majority of patients prefer the once-monthly regimen because it is "easier to follow for a long time" (Emkey, Unpublished data). Given that approximately 50% of patients treated for osteoporosis remain adherent to therapy at 1 year [49,50], strategies must be advanced to support better adherence for women with osteoporosis. While many factors impact adherence to bisphosphonates such as dosing frequency, difficult to tolerate side effects, and complexity of the treatment protocol, it is likely that the reduced medication burden offered by a once-monthly formulation can have a positive impact.

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FL-ALN to specific markers of fluid-phase endocytosis (TRITC-dextran), adsorptive endocytosis (wheat germ agglutinin-TAMRA) and receptor-mediated endocytosis (transferrin-TAMRA). Only TRITC-dextran showed a marked degree of co-localisation with FL-ALN, suggesting that a major component of BP uptake is mediated by fluid-phase endocytosis.

Using flow cytometry, J774 cells were found to markedly accumulate FL-ALN within 4 hours. Consistent with our previous findings, molar excess of the non-N-BP CLO dramatically inhibited the vesicular uptake of 100μM FL-ALN. Co-treatment of J774 cells with FL-ALN and 250μM CLO inhibited uptake of FL-ALN by 90%. This inhibitory effect of CLO was not due to inhibition of fluid-phase endocytosis, since CLO did not affect the uptake of FITC-dextran.

Since BPs are non-hydrolysable analogues of pyrophosphate (PP_i) we hypothesised that PP_i may also compete with BPs for cellular uptake. Co-treatment of J774 cells with 250μM PP_i decreased FL-ALN uptake by 76%. Due to the high affinity of BPs for divalent ions (such as Ca^{2+}), we investigated whether the inhibitory effect of CLO or PP_i was due to Ca^{2+} chelation. Whilst molar excess Ca^{2+} ions stimulated FL-ALN uptake, 500μM EGTA (a Ca^{2+} chelator) inhibited FL-ALN uptake by 96%, which was reversed in the presence of 2mM Ca^{2+}. Supplementation of 250μM CLO or PP_i with molar excess (1mM) Ca^{2+} partially prevented the inhibitory effect of CLO, but not PP_i, on FL-ALN uptake.

These observations show that cellular uptake of BPs can occur by fluid-phase endocytosis. However, there appears to be a specific recognition step prior to endocytosis that is dependent on Ca^{2+} and can be blocked by competition with PP_i or other BPs, such as CLO.

Disclosures: K. Thompson, None.

M431

Fluvastatin Prevents Bisphosphonate-Induced Vγ9Vδ2 T-Cell Activation and Proliferation *In Vitro*. K. Thompson, M. J. Rogers. Medicine & Therapeutics, University of Aberdeen, Aberdeen, United Kingdom.

An acute phase response is the major adverse effect of intravenously-administered nitrogen-containing bisphosphonates (N-BPs) and is associated with the activation (TNFα and IFNγ release) and proliferation of the major subset of γ,δ-T cells in humans (Vγ9Vδ2$^+$ subset). We, and others, have recently reported that the stimulatory effects of N-BPs on γ,δ-T cell proliferation in cultures of human PBMCs are most likely due to inhibition of FPP synthase, an enzyme in the mevalonate pathway. By this mechanism, N-BPs cause the accumulation of upstream isoprenoid lipids such as IPP, which then directly activate Vγ9Vδ2$^+$-T cells. N-BPs, such as zoledronic acid (ZOL), stimulate γ,δ-T cell proliferation in human PBMC cultures with a similar order of potency to the order of potency for inhibition of FPP synthase. Mevastatin, by inhibiting HMG-CoA reductase, can abrogate the stimulatory effects of N-BPs on γ,δ-T cells by preventing the N-BP-induced accumulation of IPP.

Treatment of PBMC cultures with 1μM ZOL for 7 days caused an ~8-fold increase in the proportion of γ,δ-T cells in the CD3$^+$ population. This proliferative effect of ZOL was decreased by >75% when PBMCs were simultaneously treated with 1μM fluvastatin (FLU). Consistent with this, 1μM ZOL caused a marked increase in the proportion of Vγ9Vδ2$^+$-T cells in the γ,δ-T cell population from ~70% (+/-9.1%) in naïve cultures to 98.6% (+/-1.6%) after 7 days treatment. Simultaneous treatment with FLU reduced the ZOL-induced increase in the proportion of Vγ9Vδ2$^+$-T cells to 86% (+/- 2.9%). The inhibitory effect of FLU could be abolished by replenishing cells with mevalonate, suggesting that FLU prevents Vδ2$^+$-T cell proliferation by inhibiting HMG-CoA reductase and preventing ZOL-induced accumulation of IPP.

Although the concentration of ZOL used in this study is similar to the C_{max} following intravenous administration to patients *in vivo* (1μM), plasma concentrations decrease rapidly with a $t_{\frac{1}{2}}$ of <2hrs. Therefore, the effectiveness of a short pulse of ZOL for inducing IFNγ release in PBMC cultures was investigated. A 2hr pulse of 1μM ZOL induced a 10.3-fold (+/-0.7) increase in IFNγ release from PBMCs after 48hrs. A simultaneous 2hr pulse with 1μM FLU markedly decreased ZOL-induced IFNγ release by >70%. When FLU was present for the entire 48hr period, FLU was only slightly more effective at preventing the ZOL-induced IFNγ release than when present only for the 2hr ZOL pulse, suggesting that sufficient FLU is internalised by PBMCs within a 2hr period to prevent the accumulation of IPP resulting from a clinically relevant exposure to ZOL. Co-administration of FLU with intravenous N-BPs may therefore provide a means for preventing the acute-phase response *in vivo*.

Disclosures: K. Thompson, Novartis Pharma AG 2.

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Once Monthly Dosing Increases the Proportion of Patients who Respond to Oral Ibandronate: 1-Year Results from MOBILE. R. Emkey[1], D. Felsenberg[2], J. J. Stepan[3], C. Hughes*[4], E. Dumont*[5], P. Van der Auwera*[4], R. R. Recker[6]. [1]Radiant Research, Wyomissing, PA, USA, [2]Charite - Campus Benjamin Franklin, Berlin, Germany, [3]Charles University, Prague, Czech Republic, [4]F. Hoffmann-La Roche Ltd, Basel, Switzerland, [5]GlaxoSmithKline, Collegeville, PA, USA, [6]Creighton University, Omaha, NE, USA.

Studies of antiresorptive agents indicate that 1-year threshold values for treatment-induced increases in BMD and decreases in BCM predict for antifracture efficacy.[1] Ibandronate (Bonivа®) is a potent, nitrogen-containing BP with antifracture efficacy when given daily or intermittently.[2] A 2-year, randomized, double-blind, phase III, non-inferiority study (MOBILE) is comparing the efficacy and safety of 50/50mg (single doses on consecutive days), 100mg (single day) and 150mg (single day) monthly oral ibandronate with oral daily ibandronate (2.5mg; 3-year vertebral fracture risk reduction: 52%) in 1,609 women with PMO. After 1 year, a prespecified analysis examined the proportion of patients in each arm achieving increases in: lumbar spine (LS) BMD above baseline or 6%; total hip (TH) BMD above baseline or 3%; both LS and TH BMD above baseline. The proportion of patients achieving decreases in sCTX below defined threshold values was also examined.

After 1 year, the majority of patients achieved increases in LS or TH BMD above baseline (**Table**). Compared with the daily arm, significantly more patients achieved increases above baseline in the 150mg arm for LS BMD and the 100mg and 150mg arms for TH BMD. Likewise, more patients in the 100mg and 150mg arms achieved substantial increases in LS BMD (>6%) and TH (>3%) BMD than in the daily arm. In addition, most participants achieved increases in both LS and TH BMD above baseline ($p \leq 0.001$ for 100mg and 150mg vs 2.5mg). In the analysis of sCTX, a significantly greater proportion of patients in the 150mg arm consistently achieved decreases in sCTX of >30%, >50% and >70%, respectively, compared with the daily arm. In summary, a larger proportion of women receiving 100mg and 150mg monthly oral ibandronate achieve increases in LS and/or TH BMD after 1 year versus those receiving daily ibandronate. Moreover, compared with daily, significantly more patients receiving 150mg ibandronate achieve threshold values for sCTX.

1. Hochberg MC, et al. J Clin Endocrinol Metab 2002;87:1586-92.
2. Chesnut CH, et al. J Bone Miner Res (In press).

Table. Proportion (%) of participants considered responders to daily or monthly ibandronate.

	Daily ibandronate	Monthly ibandronate		
Relative change (%) in BMD	2.5mg (n=318)	50/50mg (n=330)	100mg (n=315)	150mg (n=327)
LS BMD >baseline	84.0	87.8	86.5	91.3*
LS BMD >6%	24.2	30.5	32.2*	35.3*
TH BMD >baseline	76.7	81.9	87.1†	90.0†
TH BMD >3%	34.9	38.0	43.4*	48.4†
LS BMD + TH BMD >baseline	65.7	73.2*	77.7†	83.9†

*p<0.05 vs 2.5mg
†p≤0.001 vs 2.5mg

Disclosures: R. Emkey, F. Hoffmann-La Roche Ltd 2.

M433

Relative Change in Bone Mineral Density Is a Valid Surrogate for Antifracture Efficacy with Ibandronate. S. Epstein[1], H. Huss*[2], K. M. Wilson*[3], R. C. Schimmer[3]. [1]Mt Sinai Medical Center, New York, NY, USA, [2]., Levekusen, Germany, [3]F. Hoffmann-La Roche Ltd, Basel, Switzerland.

Predefined statistical analyses of the findings from recent antifracture studies of oral and intravenous ibandronate in postmenopausal osteoporosis demonstrate a reduction in risk of vertebral fracture that is significantly associated with improvements in BMD.[1,2] In light of these positive findings, an additional statistical analysis[3] was performed to validate relative change (%) from baseline in BMD as a surrogate marker for predicting 3-year VF RR with ibandronate (using total hip and lumbar spine BMD after 1, 2 and 3 years). The following criteria were used to evaluate surrogacy: (1) BMD is affected by treatment; (2) fracture incidence is affected by treatment; (3) BMD is prognostic for fracture; and (4) the proportion (p) of the 3-year antifracture effect explained by relative change (%) from baseline in BMD at each time point. For criteria 1-3, parameter estimates were produced using simple logistic regression models. When the studies were considered separately, findings were variable due to the small sample sizes. However, when the data were pooled, robust findings were reported. Notably, the criteria for surrogacy (outlined above; 1-3) were fulfilled for all analyzed surrogate endpoints for 3-year VF RR (**Table**). In addition, values for p (criterion 4) indicated that relative change (%) from baseline in total hip and lumbar spine BMD after 2 and 3 years explained a substantial proportion of the 3-year antifracture effect with ibandronate (**Table**). Importantly, values were similar to those obtained for other widely accepted surrogate endpoints. In summary, while not providing a complete explanation for antifracture efficacy, these findings highlight the utility of using relative change (%) from baseline in total hip and lumbar spine BMD after 2 and 3 years as surrogate markers for 3-year VF RR with ibandronate.

1. Wasnich R, et al. J Bone Miner Res 2003;18:S160 (Abstract SA353).
2. Miller P, et al. ASBMR 2004 (In submission).
3. Prentice RL. Stat Med 1989;8:431-40.

Table. Proportion of 3-year antifracture effect explained by relative change (%) in BMD

Surrogate	Year	Proportion of antifracture effect explained by surrogate
Relative change (%) from baseline in total hip BMD	1	14%*
	2	24%*
	3	37%*
Relative change (%) from baseline in lumbar spine BMD	1	6%*
	2	23%*
	3	27*

*Endpoints fulfilling criteria for surrogacy

Disclosures: S. Epstein, F. Hoffmann-La Roche Ltd 5.

Once-monthly dosing increases the proportion of patients who respond to oral bisphosphonate therapy: results from MOBILE

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SUMMARY

- Maintaining and increasing bone mineral density (BMD) and normalizing bone resorption levels are important therapeutic objectives in postmenopausal osteoporosis.
- A prospective 'responders' analysis of the findings from the MOBILE study of monthly and daily oral ibandronate (Boniva™) examined the proportion of patients achieving increases in lumbar spine and/or total hip BMD above baseline and threshold values correlated with antifracture efficacy as secondary efficacy endpoints (6% and 3%, respectively).
- A post-hoc analysis also considered the proportion of patients achieving clinically relevant threshold values for median change (%) from baseline in serum CTX (sCTX).
- Versus the daily arm, significantly more patients achieved increases above baseline in the
  - 150mg arm for lumbar spine BMD
  - 150mg and 100mg arms for total hip BMD
  - 150mg and 100mg arms for the combined endpoints.
- A greater proportion of patients in the 150mg and 100mg arms also achieved more substantial increases in lumbar spine BMD (>6%) and total hip BMD (>3%) than in the daily arm.
- With respect to sCTX, the majority of patients achieved decreases of >30% and >50%, and a substantial proportion achieved decreases of >70%
  - as for the BMD endpoints, a significantly larger proportion of patients in the 150mg arm achieved predefined threshold values than in the daily arm.
- Overall, these findings demonstrate that the majority of patients achieve clinically meaningful responses to both monthly and daily oral ibandronate therapy.
- However, compared with daily dosing, a greater proportion of patients receiving once-monthly ibandronate achieve positive therapeutic outcomes.

INTRODUCTION

- Baseline levels of BMD and biochemical markers of bone turnover are strongly predictive of fracture risk in postmenopausal osteoporosis.[1]
- Likewise, antiresorptive treatment-related increases in BMD and decreases in biochemical markers of bone turnover are predictive of vertebral[2] and non-vertebral[3] antifracture efficacy.
- Ibandronate, a potent, nitrogen-containing bisphosphonate, is proven to substantially increase BMD, decrease bone turnover and reduce fracture risk in postmenopausal osteoporosis when administered daily or intermittently (between-dose interval >2 months) as an oral medication.[4]
- The equivalent efficacy and comparable safety profile of monthly and daily oral ibandronate regimens was also recently demonstrated in the MOBILE study.[5]
- A predefined 'responders' analysis of the MOBILE study examined the proportion of patients in the monthly and daily treatment arms achieving gains in lumbar spine and/or total hip BMD above baseline and threshold values correlated with antifracture efficacy as secondary efficacy endpoints (6% and 3%, respectively).[5]
- A post-hoc analysis also considered the proportion of patients achieving predefined and clinically relevant levels of sCTX suppression.[6]
- The findings of these analyses are reported below.

METHODS

Study design

- Multinational, double-blind, randomized, phase III, non-inferiority study.
- Women (aged 55–80 years; ≥5 years since menopause [YSM]) with postmenopausal osteoporosis (lumbar spine [L2–L4] BMD T-score <–2.5 and ≥–5).
- 2.5mg daily oral ibandronate, or 50/50mg (single doses on consecutive days), 100mg (single day) or 150mg (single day) monthly oral ibandronate.
- Study medication taken after an overnight fast, immediately upon rising and 1 hour before food, non-study medications and fluids other than water.
- Daily calcium (500mg) and vitamin D (400IU) supplements were provided.

Study endpoints

- The proportion of patients achieving mean increases in lumbar spine BMD above baseline and 6%, total hip BMD above baseline and 3%, and lumbar spine and total hip BMD above baseline after 1 year was a secondary efficacy endpoint.
- The proportion of participants achieving median decreases in sCTX of >30%, >50% and >70% was also explored.

Statistical analysis

- The per-protocol (PP) population was the primary analysis population for all efficacy endpoints.
- Participants were excluded from the PP analysis in the event of: a biased BMD assessment, a baseline T-score >–2.5, an infringement of one of the study exclusion criteria, poor compliance with treatment, or an unconfirmed menopausal status.

RESULTS

Patient characteristics

- In total, 1,609 women participated in the study.
- Of these women, 1,290 fulfilled the criteria for inclusion in the PP analysis (**Table 1**).
- Baseline characteristics were well balanced (**Table 1**).

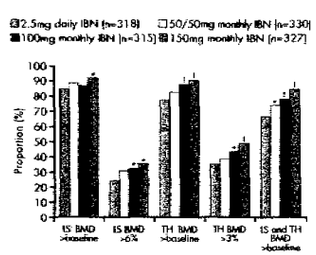
Table 1. **Patient demographics (mean; PP).**

	Dose			
	2.5mg (n=318)	50/50mg (n=330)	100mg (n=315)	150mg (n=327)
Age (years)	65	66	66	66
Weight (kg)	64	63	64	64
Height (cm)	157	157	158	158
Body mass index (kg/m²)	26	26	26	26
YSM (years)	18	18	18	18
History of previous fractures (%)	156 (49.4)	149 (45.2)	144 (45.7)	151 (46.2)
Lumbar spine (L2–L4) BMD (T-score)	–3.3	–3.3	–3.3	–3.3
Total hip BMD (T-score)	–1.8	–1.8	–1.8	–1.8
sCTX (ng/mL)*	0.485	0.520	0.510	0.500
BAP (ng/mL)*	10.545	11.080	11.445	11.520
25-OH-D (ng/mL)	25.6	24.4	25.2	24.7

*Median values

BMD responders analysis

- The findings from the prospectively defined BMD responders analysis are presented in **Figure 1**.
- After 1 year, the majority of patients achieved lumbar spine or total hip BMD gains above baseline.



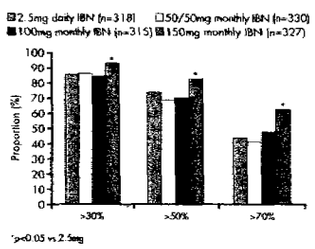
*p<0.05 vs 2.5mg; †p≤0.001 vs 2.5mg; ‡LS = lumbar spine; §TH = total hip

Figure 1. **Proportion of participants achieving predefined threshold values for mean change (%) from baseline in lumbar spine and total hip BMD (PP).**

- However, compared with the daily arm, significantly more patients achieved increases above baseline in the
  - 150mg arm for lumbar spine BMD
  - 150mg and 100mg monthly arms for total hip BMD.
- In addition, versus the daily arm, significantly more patients in the 150mg and 100mg monthly arms achieved substantial increases in BMD at the lumbar spine (>6%) and total hip (>3%).
- Moreover, significantly more patients in the 150mg and 100mg monthly ibandronate arms achieved gains in both lumbar spine and total hip BMD above baseline (p≤0.001 vs daily ibandronate).

sCTX responders analysis

- The proportion of patients achieving decreases in sCTX of >30%, >50% and >70% is presented in **Figure 2**.
- After 1 year, the majority of participants achieved decreases in sCTX of >30% and >50% (**Figure 2**).
- A substantial proportion of participants also achieved decreases in sCTX of >70% (**Figure 2**).
- Compared with the daily regimen, a significantly greater proportion of participants in the 150mg arm achieved decreases in sCTX of >30%, >50% and >70%.



*p<0.05 vs 2.5mg

Figure 2. **Proportion of participants achieving predefined threshold values for mean change (%) from baseline in sCTX (PP).**

CONCLUSIONS

- These findings demonstrate that the majority of patients achieve clinically meaningful responses to monthly and daily oral ibandronate therapy
  - most patients achieve substantial gains in BMD
  - the majority of patients achieve substantial decreases in sCTX.
- Moreover, compared with the daily oral regimen, the proportion of patients achieving positive therapeutic outcomes is significantly greater with monthly oral ibandronate.

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Monthly Oral Ibandronate Significantly Reduces Bone Resorption in Postmenopausal Osteoporosis: 1-Year Results from MOBILE. R. R. Recker[1], D. L. Kendler[2], S. Adami[3], C. Hughes*[4], E. Dumont*[5], R. C. Schimmer[4], C. Cooper[6]. [1]Creighton University, Omaha, NE, USA, [2]University of British Columbia, Vancouver, BC, Canada, [3]University of Verona, Verona, Italy, [4]F. Hoffmann-La Roche Ltd, Basel, Switzerland, [5]GlaxoSmithKline, Collegeville, PA, USA, [6]University of Southampton, Southampton, United Kingdom.

Bisphosphonate therapies are effective in normalizing the elevated rate of bone turnover associated with postmenopausal osteoporosis (PMO). Ibandronate (Boniva®) is a potent, nitrogen-containing bisphosphonate with proven antifracture efficacy when administered daily or intermittently in postmenopausal women with osteoporosis (3-year vertebral fracture risk reduction: 52% and 50%, respectively).[1] An ongoing, randomized, double-blind, phase III, non-inferiority study (MOBILE) is comparing the efficacy and safety of monthly oral 50/50mg (single doses on consecutive days), 100mg (single day) and 150mg (single day) ibandronate regimens with the proven oral daily (2.5mg) regimen in 1,609 women with PMO. In MOBILE, relative change (%) in the biochemical marker of bone resorption, sCTX, is a secondary efficacy endpoint, measured immediately prior to the scheduled ibandronate doses at 3, 6, 12 and 24 months. After 1 year, the magnitude of median sCTX suppression in the oral daily arm was 67.3% (Table). A comparable magnitude of sCTX suppression was reported in each of the monthly oral arms after 1 year (one month after dosing): 62.8%, 66.7% and 75.8% in the 50/50mg, 100mg and 150mg arms, respectively (Table). Substantial decreases in sCTX were also observed after 3 and 6 months (Table). At all assessment points, the 150mg regimen provided the greatest magnitude of sCTX suppression. In summary, monthly oral ibandronate rapidly suppresses bone resorption to normal levels within 3 months of initiation, and maintains this magnitude of suppression with continued therapy. Monthly oral ibandronate also provides a comparable magnitude of sCTX suppression to that observed with an oral daily ibandronate regimen of proven antifracture efficacy (3-year vertebral fracture risk reduction: 52%). These findings indicate that monthly oral ibandronate is a highly effective alternative to more frequently administered bisphosphonates in PMO.

1. Chesnut CH, *et al. J Bone Miner Res (In press).*

Table. Median relative change (%) from baseline in sCTX

	Daily ibandronate	Monthly ibandronate		
Month	2.5mg (n=318)	50/50mg (n=330)	100mg (n=315)	150mg (n=327)
3	-53.6	-50.0	-53.2	-66.1
6	-63.5	-60.7	-63.2	-73.4
12	-67.3	-62.8	-66.7	-75.8

Disclosures: R.R. Recker, F. Hoffmann-La Roche Ltd 2, 5.

Monthly oral ibandronate significantly reduces bone resorption in postmenopausal osteoporosis: 1-year results from MOBILE

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[1]Crichton University, Dundee, Scotland, UK; [2]University of British Columbia, Vancouver, Canada; [3]University of Verona, Verona, Italy; [4]Hoffmann-La Roche Inc., Nutley, New Jersey, USA; [5]Robert Wood Johnson Medical School, Piscataway, New Jersey, USA; [6]Aarhus University Hospital, Aarhus, Denmark; [7]Roche Products Ltd, Welwyn Garden City, Hertfordshire, UK; [8]Roche Products Ltd, Welwyn Garden City, Hertfordshire, UK

SUMMARY

- Changes in biochemical markers of bone turnover with less frequent than weekly bisphosphonate dosing schedules are yet to be fully explored.
- Ibandronate (Boniva™) is a potent, nitrogen-containing bisphosphonate with proven antifracture efficacy when administered as an oral medication, either continuously (daily) or intermittently with extended between-dose intervals (3-year vertebral fracture risk reduction: 52% and 50%, respectively).[1]
- In the MOBILE study, 50/50mg, 100mg and 150mg monthly oral ibandronate regimens were shown to be as effective (based on bone mineral density (BMD) endpoints) as the daily oral ibandronate regimen (2.5mg) in 1,609 women with postmenopausal osteoporosis.[2]
- Substantial and comparable decreases in the biochemical marker of bone resorption, serum CTX (sCTX), were also observed in the monthly and daily treatment arms after 1 year (secondary efficacy endpoint).
- Additional retrospective analyses revealed pronounced reductions in the biochemical marker of bone formation, bone alkaline phosphatase (BAP), which were within the ranges commonly associated with currently licensed oral bisphosphonates.
- These findings further demonstrate the comparable efficacy of monthly and daily oral ibandronate regimens in postmenopausal osteoporosis and offer further insights into the biomarker responses associated with less frequently administered bisphosphonates.

INTRODUCTION

- Continuously administered oral bisphosphonates (e.g. daily or weekly) are highly effective in normalizing the elevated rate of bone resorption commonly associated with postmenopausal osteoporosis.
- However, experience with less frequently administered bisphosphonates is less well documented.
- Ibandronate has proven antifracture efficacy when administered continuously (daily), and also when administered intermittently with extended dosing intervals.[1]
- In the MOBILE study, 50/50mg, 100mg and 150mg monthly oral ibandronate regimens were shown to be as effective (based on BMD endpoints) as the daily oral ibandronate regimen (2.5mg, 3-year vertebral antifracture efficacy: 52%) in 1,609 postmenopausal women with osteoporosis.[2]
- Here, we describe the effect of monthly and daily oral ibandronate on the biochemical marker of bone resorption, sCTX (secondary efficacy endpoint).
- The findings of a recent post-hoc analysis of the biochemical marker of bone formation, BAP, are also described.

METHODS

Study design

- Multinational, randomized, double-blind, phase III, non-inferiority study.
- Postmenopausal women aged 55–80 years (years since menopause [YSM]: ≥5 years) with osteoporosis (lumbar spine [L2–L4] BMD T-score <–2.5 and ≥–5).
- Two-years' treatment with 50/50mg (single doses on consecutive days), 100mg (single day), 150mg (single day) monthly oral ibandronate or 2.5mg daily oral ibandronate.
- Study medication taken after an overnight fast of ≥6 hours and ≥1 hour before food, non-study medications and fluids other than water.
- Supplementation with daily oral calcium (500mg) and vitamin D (400IU).

Study endpoints

- Median change (%) from baseline in sCTX was a secondary efficacy endpoint (secondary efficacy endpoint).
- Median change (%) from baseline in BAP was analyzed retrospectively.
- sCTX and BAP concentrations were assessed in blood samples taken at baseline, 3, 6 and 12 months
  - all samples were taken immediately prior to the next scheduled dose of study medication and after an overnight fast of ≥6 hours.

Statistical analysis

- All efficacy parameters were evaluated in the per protocol (PP) analysis population
  - participants were excluded from the PP analysis in the event of: a biased BMD assessment, a baseline T-score >–2.5, an infringement of one of the study exclusion criteria, poor compliance or an unconfirmed menopausal status.
- Confirmatory intent-to-treat (ITT) analyses were also performed for all efficacy endpoints.

RESULTS

Patient characteristics

- A total of 1,609 women were randomized into the study.
- Of these, 1,290 women fulfilled the criteria for inclusion in the PP analysis (**Table 1**).

Table 1. ***Patient demographics (mean; PP).***

	Dose			
	Daily (n=318)	**50/50mg (n=330)**	**100mg (n=315)**	**150mg (n=327)**
Age (years)	65	66	66	66
Weight (kg)	64	63	64	64
Height (cm)	157	157	158	158
Body mass index (kg/m²)	26	26	26	26
YSM (years)	18	18	18	18
History of previous fractures (%)	156 (49.4)	149 (45.2)	144 (45.7)	151 (46.2)
Lumbar spine (L2–L4) BMD (T-score)	–3.3	–3.3	–3.3	–3.3
Total hip BMD (T-score)	–1.8	–1.8	–1.8	–1.8
sCTX (ng/mL)*	0.485	0.520	0.510	0.500
BAP (ng/mL)*	10.545	11.080	11.445	11.520
25-OH-D (ng/mL)	25.6	24.4	25.2	24.7

*Median values

- The baseline characteristics of the PP analysis population were comparable across all study groups (**Table 1**).

sCTX

- Substantial and similar decreases in sCTX were observed in all treatment arms after 1 year (**Figure 1**).
- Pronounced decreases in sCTX were also observed by the first measurement, at 3 months (**Figure 1**).
- At all timepoints the 150mg monthly oral regimen provided the greatest magnitude of sCTX suppression.
- Comparable findings were obtained for the ITT population.

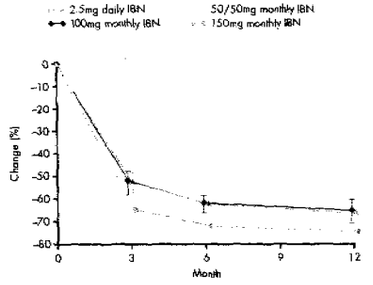


Figure 1. **Time course of median change (%) from baseline in sCTX with monthly and daily oral ibandronate (PP).**

BAP

- Pronounced and sustained decreases in BAP were also observed in all treatment arms (**Figure 2**).
- All measurements were within the ranges commonly observed with more frequently administered nitrogen-containing bisphosphonates.[3,4]

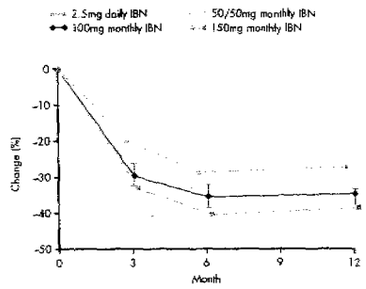


Figure 2. **Time course of median change (%) from baseline in BAP with monthly and daily oral ibandronate (PP).**

CONCLUSIONS

- Compared with a daily oral dosing schedule, monthly oral ibandronate regimens provide robust and similar suppression of sCTX and BAP in women with postmenopausal osteoporosis.
- All measurements of BAP were within the ranges commonly observed with current nitrogen-containing bisphosphonates.[3,4]
- These findings
  - further demonstrate the comparable efficacy of monthly and daily oral ibandronate regimens in postmenopausal osteoporosis
  - offer further insights into the biomarker response associated with less frequently than weekly administered oral ibandronate.

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US006143326A

United States Patent [19]

Möckel et al.

[11] Patent Number: 6,143,326

[45] Date of Patent: *Nov. 7, 2000

[54] **ORAL PHARMACEUTICAL PREPARATION CONTAINING IBANDRONAT**

[75] Inventors: **Jörn Möckel**, Heidelberg; **Rolf-Dieter Gabel**, Schwetzingen; **Heinrich Woog**, Laudenbach, all of Germany

[73] Assignee: **Roche Diagnostics GmbH**, Mannheim, Germany

[*] Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

[21] Appl. No.: **09/147,149**

[22] PCT Filed: **Apr. 21, 1997**

[86] PCT No.: **PCT/EP97/01940**

§ 371 Date: **Nov. 25, 1998**

§ 102(e) Date: **Nov. 25, 1998**

[87] PCT Pub. No.: **WO97/39755**

PCT Pub. Date: **Oct. 30, 1997**

[30] **Foreign Application Priority Data**

Apr. 20, 1996 [DE] Germany 196 15 812

[51] **Int. Cl.**[7] **A61K 9/36**

[52] **U.S. Cl.** **424/482**; 424/480

[58] **Field of Search** 424/480, 482

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Primary Examiner—Thurman K. Page
Assistant Examiner—A. Berman
Attorney, Agent, or Firm—Arent Fox Kintner Plotkin Kahn

[57] **ABSTRACT**

The invention is directed to well-tolerated pharmaceutical compositions for oral application, containing ibandronate or a physiologically tolerable salt thereof as active substance, the administration form consisting of an active substance-containing inner portion enclosed in such fashion by a coat free of active substance that rapid release of the active substance takes place.

3 Claims, No Drawings

ORAL PHARMACEUTICAL PREPARATION CONTAINING IBANDRONAT

This is a 371 of PCT/EP97/01940 filed Apr. 21, 1997 which claims priority from German application DE19615812.5 filed Apr. 20, 1996.

The invention relates to pharmaceutical formulations of ibandronate or its physiologically tolerable salts for oral application, and to processes for producing same.

The active substance ibandronaic acid (1-hydroxy-3-(N-methyl-N-pentyl)aminopropyl-1,1-diphosphonic acid) and its salts (ibandronates), respectively, are among the class of diphosphonic acids which, in particular, are of interest in the treatment of bone diseases and particular disorders in the calcium metabolism such as hypercalcaemia, osteoporosis, tumor osteolysis or Paget's disease. In the treatment of the diseases mentioned, these active substances must be administered frequently and over a long period of time and therefore, the aim should be especially oral application in addition to intravenous application since it is the former which is more accepted by many patients.

Fundamentally, however, oral treatment is generally complicated by the well-known problems with oral tolerability of diphosphonic acids. Diphosphonic acids or their physiologically safe salts, and particularly aminodiphosphonic acids are known to give rise to irritations of the upper gastrointestinal tract (Fleisch H., Bisphosphonates in Bone Disease, Herbert Fleisch, Bern 1993, pp. 126–131). The same applies for diphosphonates which are also ingested at relatively low dosages of, e.g., less than 50 mg per single administration form. WO 93/09785 points out that the active substance risedronate ([1-Hydroxy-2-(3-pyridinyl) ethylidene]bisphosphonate), for example, may give rise to erosions and ulcerations in the upper sections of the digestive tract. Various references allude to the gastrointestinal intolerability of the active substances pamidronate (Dodwell D. et al., Biochemical Effects, Antitumor Activity and Pharmacokinetics of Oral and Intravenous Pamidronate (APD) in the Treatment of Skeletal Breast Cancer, Br. J. Cancer 62, 496 (1990)) and tiludronate (Reginster J. Y., Efficacy and Tolerability of a New Formulation of Oral Tiludronate (Tablet) in the Treatment of Paget's Disease of Bone, J. Bone Miner. Res. 9, 615–619 (1994)). In addition, it is also well-known that motility disorders may occur when swallowing the tablets and/or the tablets to be ingested get stuck due to the particular anatomic situation in the oesophagus. This may give rise to odynophagia or oesophageal strictures as well. Frequently, this is the case with elderly patients or with patients who, due to their disease, are forced to take the required tablets predominantly in a lying position.

Accordingly, in order to solve these problems, the art demanded that fundamentally, orally available administration forms be coated with a gastric juice-resistant film so that the active substance is released only subsequent to the passage through the stomach and thus, irritations of the stomach and the oesophagus would be avoided. For example, WO 95/08331 describes administration forms by which it is possible to reduce the irritating potential of alendronate and other diphosphonates in oral application.

Due to the above-described oral intolerability of diphosphonates, there has been a search for more tolerable administration forms for a number of these active substances. In particular, oral administration forms coated with gastric juice-resistant coatings have been developed in this context. Such coatings are the choice in protecting the upper sections of the gastrointestinal tract, particularly the oesophagus or the stomach, from intolerable active substances. These gastric juice-resistant coatings on solid oral administration forms dissolve only at higher pH values of about 5.5 on, so that in the acidic gastric medium, being at a pH value far below 5.5, no active substance will be released from the administration form and thus, the stomach is protected from irritations caused by the active substance. As no active substance is released in the stomach, it is possible at the same time to prevent oesophagitis or other irritations of the oesophagus caused by the refluxing gastric contents containing active substance. As a consequence, DE 59 005 517 (EP 421,921) describes a gastric juice-resistant oral administration form for pamidronate which is suitable in reducing the risk of gastric ulcerations. Furthermore, WO 93/09785 illustrates such an administration form for risedronate, WO 95/08331 for alendronate and other diphosphonates.

The potential advantages of the gastric juice-resistant administration forms are contrasted by a number of drawbacks. Thus, resorption with these administration forms may be reduced as compared to forms releasing in a pH-independently rapid fashion, or resorption is substantially more variable as compared to conventional forms, thus impairing or jeopardizing therapeutical safety. Therefore, there is a demand in alternative administration forms for these active substances in order to avoid the disadvantages of the gastric juice-resistant forms and nevertheless, be capable of providing sufficient protection from these aminobisphosphonates having aggressive effects on the gastric mucosa.

Surprisingly, it was found that improved oral tolerability in the case of the ibandronate active substance is already achieved when peroral administration forms are coated with an adjuvant coating or film in such fashion that the active substance is dissolved within a short period of time and correspondingly high local concentrations of active substance are achieved in the stomach. The film dissolving upon contact with digestive juice is preferably a coating which dissolves pH-independently. The adjuvant coating may be coated using methods common in pharmaceutical technology. Although this coating does not prevent dissolution of ibandronate in the stomach, it was surprising that no significant side effects were observed in clinical studies using ibandronate even at high dosages. Despite the fact that the administration forms are coated with a film which quickly releases the active substance, there are no irritations in the oesophagus when swallowing the tablets, and oesophagitis does not occur. This is particularly advantageous since the administration forms of the invention are also well-tolerated by patients lying in bed.

According to the invention, solid oral formulations of ibandronate are provided, consisting of a core containing the active substance, which is coated with an adjuvant coating free of active substance, which either dissolves independently of the pH value or is removed from the solid oral formulation upon contact with digestive juice. In this way, relatively rapid disintegration of the drug form and release of the active substance within a short period of time are ensured, whereby high local concentrations of the active substance are achieved. The coating may be applied using methods such as film coating, press coating, tablet coating, encapsulating or micro-encapsulating. The release of active substance from the appropriately coated solid administration forms for oral application, such as film tablets, coated tablets, laminated tablets, capsules, or microcapsules, takes place more rapidly as compared to the gastric juice-resistant administration forms. According to the invention, at least 30% of the contained ibandronate dose, but preferably at

least 75% and, in particular, at least about 85% is released rapidly and independently of the pH value within the physiological pH range. Preferably, the time period required to achieve these release percentages is less than 2 hours, more preferably less than 1 hour, with about 1–30 minutes being particularly preferred. It is particularly preferred that the release is about 80–90% within a time period of up to 15 minutes. Conveniently, the release of active substance is estimated within the scope of an in vitro experiment according to well-known standardized procedures.

Surprisingly, rapid release of the active substance does not result in the undesirable side effects usually known for diphosphonic acids as described above, despite the high local concentrations of active substance (i.e., despite the high gradient of active substance) thereby generated in the stomach. Rather, it was found that despite the rapid release of active substance, the problem of occurring gastrointestinal disorders is avoided, quite surprisingly. Furthermore, it has been observed that among patients treated with such rapidly releasing administration forms of ibandronate, there were significantly less cases of nausea, vomiting, pain or diarrhoea than otherwise observed when administering aminobisphosphonates.

The coatings with rapid release of active substance in the meaning of the invention can be applied to all the suitable peroral administration forms such as tablets, capsules, coated tablets, pellets, granulates or powders. These administration forms consist of mixtures of active substances with pharmaceutical adjuvants or of pure active substances. Coating may be performed using various methods common in pharmacy. For example, suitable methods use tablet coating units, film coating units, tablet presses for press coating, encapsulating machines, or micro-encapsulating units, such as facilities for spray freezing and spray embedding, facilities for producing simple or complex coacervates.

In the meaning of the invention, pharmaceutically common or physiologically safe polymers are possible as film-forming agents. Film-forming agents in the meaning of the invention are derived from, e.g., the groups of cellulose derivatives, dextrins, starches and starch derivatives, polymers based on other carbohydrates and derivatives thereof, natural gums such as gum arabic, xanthans, alginates; polyacrylic acid, polyvinyl alcohol, polyvinyl acetate, polyvinylpyrrolidone, polymethacrylates and derivatives thereof (Eudragit®), chitosan and derivatives thereof, shellac and derivatives thereof. In addition to these film-forming agents, substances from the class of wax and fat substances may be used to produce the coatings according to the invention.

Preferably, the soluble alkyl- or hydroxyalkylcellulose derivatives such as methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, methylhydroxyethylcellulose, methylhydroxypropylcellulose, or sodium carboxymethylcellulose are possible as cellulose derivatives. In a preferred variant of an embodiment of the invention, methylhydroxypropylcellulose is employed. The usual cellulose derivatives suitable for pharmaceutical purposes, with varying degrees of substitution and/or varying molecular weights corresponding to varying viscosity levels of the aqueous solutions, may be used as suitable film-forming agents on the basis of cellulose. Likewise, insoluble cellulose derivatives such as ethylcellulose may be employed.

In the case of polymethacrylates, cationic copolymerizates of dimethylaminoethyl methacrylate with neutral methacrylic esters (Eudragit® E), copolymerizates of acrylic and methacrylic esters having a low content of quaternary ammonium groups (described in "Ammonio Methacrylate Copolymer Type A or Type B" USP/NF, Eudragit® RL and RS, respectively), and copolymerizates of ethyl acrylate and methyl methacrylate with neutral character (in the form of an aqueous dispersion, described in "Polyacrylate Dispersion 30 Per Cent" Ph. Eur., Eudragit® NE 30 D) are possible.

Similarly, the use of film-forming agents usually employed in the production of gastric juice-resistant films is possible as long as pH-independently rapid release of the active substance from the appropriately coated administration form, as described above, is ensured, e.g., by a thin layer thickness of the coating or other measures such as an extremely high percentage of pore-forming agents or the like. Anionic copolymerizates of methacrylic acid and methyl methacrylate (described in "Methacrylic Acid Copolymer, Type C" USP/NF, Eudragit® L and S, respectively, or in the form of the Eudragit® L 30 D aqueous dispersion), acidic cellulose derivatives such as cellulose acetate phthalate, cellulose acetate trimellitate and methylhydroxypropylcellulose phthalate, polyvinyl acetate phthalate, etc. may be used as such films.

In principle, all the film-forming agents may be employed alone as well as in mixtures of two or more filmforming agents.

If required, the films may contain additional adjuvants such as plasticizers, pore-forming agents, filling agents, colorants, pigments, antifoam agents, antistick agents, and the like.

According to the invention, polymers and adjuvants possibly required in addition, as were described in the preceding paragraph, are possible for press coating as far as they can be processed by means of press coating technology. In addition, all the pharmaceutically common or physiologically tolerable adjuvants which are suited to form a closed coat by press coating on the drug forms to be covered may be used in the meaning of the invention. In particular, these include adjuvants as are common in conventional tabletting, specifically filling agents from the group of carbohydrates such as lactose, saccharose, glucose and other sugars, microcrystalline cellulose, starches and starch derivatives, sugar alcohols such as mannitol, sorbitol, xylitol, inorganic filling agents such as phosphates and carbonates. According to the invention, other adjuvants as required in the production of conventional tablets, such as binding agents, disintegrants, flow agents, release agents, taste improvers, pigments, and coloring agents may be contained in addition to the filling agents.

According to the invention, all the adjuvants described above may be employed for tablet coating, in principle. In addition, special adjuvants for tablet coating may be employed according to the invention, such as palatinite, bentonite, calcium sulfate as filling agents, polyethylene glycol or polyethylene glycol fatty acid esters as release agents, colloid silicic acid as drying agent and structuring agent, magnesium oxide as spreading powder, pharmaceutically common or physiologically safe fats and waxes as glossing agents.

In the meaning of the invention, all the pharmaceutically common capsules such as gelatin hard capsules, soft gelatin capsules, starch capsules are possible as capsules. The capsules may be filled with powders, granulates, pellets or tablets. In general, all the pharmaceutically common solid, liquid and semi-solid formulations may be filled into the capsules of the invention.

For micro-encapsulating the active substance or formulations of the active substance, all the polymeric film-

forming agents mentioned above may be used according to the invention. Here, the polymers may be used alone as well as in mixtures of multiple polymers, and also together with other adjuvants, if necessary.

In the following, the invention will be illustrated by way of embodiments which are not intended as limitation.

For example, The ibandronate active substance is employed in amounts of 0.1–100 mg per single dosage unit. Preferably, the dosage is at least ca. 1 mg, 5 mg, 10 mg, or 20 mg as lower limit for the amount of active substance in a single administration form. The upper limit is about 250 mg, particularly 100 mg and 50 mg, respectively.

EXAMPLE 1

Ibandronate-containing core: Ibandronate dose [mg] in 200 mg tablet core:	10.0	20.0	50.0
Ibandronate-free coat [mg]:			
Methylhydroxypropylcellulose	5.1425	5.1425	5.1425
Titanium dioxide	2.4650	2.4650	2.4650
Macrogol	1.5000	1.5000	1.5000
Talc	0.8925	0.8925	0.8925
Total film coated	10.0000	10.0000	10.0000

Film-coating is carried out in common apparatus. Coating conditions: tablet charge 140 kg; feed air temperature: 60° C.

EXAMPLE 2

Ibandronate-containing core: Ibandronate dose in 100 mg tablet core [mg]:	0.1	2.5	5.0
Ibandronate-free coat [mg]:			
Methylhydroxypropylcellulose	2.057	2.057	2.057
Titanium dioxide	0.986	0.986	0.986
Macrogol	0.600	0.600	0.600
Talc	0.357	0.357	0.357
Total film coated	4.000	4.000	4.000

Film-coating in a conventional 250 l tablet coating tank. Coating conditions: tablet charge 144 kg.

EXAMPLE 3

Ibandronate-containing core: Ibandronate dose [mg] in 200 mg tablet core:	10.0	20.0	50.0
Ibandronate-free coat [mg]:			
Talc	2.00	2.00	2.00
Lactose	1.40	1.40	1.40
Methylhydroxypropylcellulose	0.80	0.80	0.80
Titanium dioxide	0.80	0.80	0.80
Macrogol	0.40	0.40	0.40
Ethyl methyl methacrylate copolymer*	0.04	0.04	0.04
Polysorbate	0.04	0.04	0.04
Total film coated	5.48	5.48	5.48

*Employed in the form of Eudragit ™ NE 30 D as an aqueous dispersion.

Film-coating in a conventional 15 l tablet coating tank. Coating conditions: tablet charge 13.0 kg.

EXAMPLE 4

Ibandronate-containing core: Ibandronate dose [mg] in 86 mg tablet core:	10
Ibandronate-free coat [mg]:	
Saccharose	37.844
White clay	8.138
Talc	1.000
Macrogol	2.848
Glucose syrup	2.035
Titanium dioxide	1.628
Polyvidone	0.407
Montan glycol wax	0.100
Total tablet coating applied	54.000

Tablet coating in a conventional 15 l tablet coating tank with dip pipe.

EXAMPLE 7

Ibandronate in laminated tablet	
Ibandronate-containing core:	
Final weight:	86 mg
Format of core:	7 mm in diameter, plane, with facettes
Ibandronate dose in tablet core:	10 mg
Ibandronate-free coat:	
Lactose	270 mg
Microcrystalline cellulose:	90 mg
Pressing tool:	12 mm in diameter
Final weight of laminated tablet:	446 mg

Pressing by means of a hand press using conventional procedures.

What is claimed is:

1. A method of treating a bone disease in a patient in need thereof, comprising orally administering to the patient a pharmaceutical formulation comprising a tablet core containing about 0.1 to 100 mg of ibandronate and a coating which is free of ibandronate and has the following proportional composition:

(a) about 51.425% by weight of methylhydroxypropylcellulose;

(b) about 24.650% by weight of titanium dioxide;

(c) about 15.000% by weight of polyethylene glycol; and

(d) about 8.925% by weight of talc.

2. The method of claim 1, wherein the bone disease is related to a disorder in calcium metabolism.

3. The method of claim 1, wherein the bone disease is selected from the group consisting of hypercalcemia, osteoporosis, tumor osteolysis, and Paget's disease.

* * * * *

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(54) Title: PROCESS FOR THE PREPARATION OF ORAL PHARMACEUTICAL COMPOSITIONS COMPRISING BIPHOSPHONATES

(57) **Abstract**

The invention relates to a process for the preparation of bisphonate–containing pharmaceutical compositions for oral application, wherein the active substance is wet–granulated in manner known per se in a fluidised–bed granulator using adjuvants which have no abrasive action and wherein the wet granulate is then dried in the fluidised bed, screened through a screen having a suitable mesh width and further processed by techniques known per se to form pharmaceutical compositions.

The invention is preferably used for producing pharmaceutical preparations which contain the active substance in a proportion of up to 50 mg per unit dose, preferably up to 10 mg, particularly preferably 0.1 to 5 mg and 0.1 to 2.5 mg. Ibandronate is a particularly preferred active substance, particularly in the form of Na-Ibandronate monohydrate.

The adjuvants which do not have an abrasive effect during granulation may, according to the invention, be fillers such as lactose in hydrate or anhydrate form, sugar alcohols such as mannitol; tableting adjuvants such as cellulose in microcrystalline or fibrous form; and binders such as polyvinyl pyrrolidone (Povidone USP) or cellulose ethers such as methyl hydroxypropyl cellulose. At least one adjuvant is used which acts as binder.

Preferably at least one of the adjuvants is lactose, microcrystalline cellulose or polyvinyl pyrrolidone. In a preferred embodiment 1-99% by weight lactose, 1-99% by weight microcrystalline cellulose, 0.1-20% by weight are used, particularly preferably 25-75% by weight lactose, 10-20% by weight microcrystalline cellulose, and 2-3% by weight polyvinyl pyrrolidone.

The granulate is further processed by known methods, using additional adjuvants if required, into tablets, chewing tablets, effervescent tablets, film tablets, dragees and pellets or filled into hard gelatine capsules or sachets. The adjuvants used in further processing are conventional lubricants, e.g., stearic acid, disintegrants, e.g., cross-linked polyvinyl pyrrolidone (Crospovidone USPNF), flow-regulators,

in-process control: 220.05 mg
Content of active substance found in the capsules produced in this way: 94.9% ± 1.9%
(n = 10 individual measurements)

Example 3:

Production of ibandronate 1.0 mg tablets after granulation in a fluidised bed (batch size for 60.000 tablets).

Constituents		g
Na-Ibandronate	64.14	
Lactose		4405.86
Polyvinyl pyrrolidone		150.00
Polyvinyl pyrrolidone, cross-linked (disintegrant)		300.00
Stearic acid (lubricant)		120.00
Microcrystalline cellulose		900.00
Colloidal SiO_2 (flow agent)		60.0

The amount of active substance per tablet is equivalent to 1.0 mg of free acid.

Lactose and 600 g microcrystalline cellulose were granulated with an aqueous solution of polyvinyl pyrrolidone and ibandronate in a fluidised-bed granulator (Aeromatic type). The wet granulate was dried in the fluidised bed (Aeromatic type), passed through a 1.0 mm screen, mixed with disintegrant, lubricant, flow-regulator and 300 g microcrystalline cellulose (Turbula-type mixer, mixing time 5 minutes)

and converted into tablets in a tableting press (Korsch type) having a capacity of 25,000 tablets per hour.

Set weight of tablets:	100.0 mg
Actual weight of tablets according to in-process control:	101.3 mg

Content of active substance found per tablet produced in this way: 98.3% ± 4.2% (n = 10 individual measurements).

The active substance content of the tablets was within the acceptance limits.

Example 4

Production of ibandronate 0.1 mg tablets after granulation in a fluidised bed (batch size for 150.000 tablets).

Constituents	g
Na-Ibandronate monohydrate	16.95
Lactose	11158.05
Polyvinyl pyrrolidone	375.00
Polyvinyl pyrrolidone, cross-linked (disintegrant)	750.00
Stearic acid (lubricant)	300.00
Microcrystalline cellulose	2250.00
Colloidal SiO_2 (flow agent)	150.00

The amount of active substance per tablet is equivalent to 0.1 mg of free acid.

Lactose and 1500 g microcrystalline cellulose were granulated with an aqueous solution of polyvinyl

pyrrolidone and ibandronate in a fluidised-bed granulator (Aeromatic type). The wet granulate was dried in the fluidised bed (Aeromatic type), passed through a 1.0 mm screen, mixed with disintegrant, lubricant, flow-regulator and 750 g microcrystalline cellulose (Turbula-type mixer, mixing time 10 minutes) and converted into tablets in a tableting press (Korsch type) having a capacity of 60,000 tablets per hour.

Set weight of tablets:	100.0 mg
Actual weight of tablets according to in-process control:	101.3 mg

Content of active substance found per tablet produced in this way : 98.5% ± 2.4% (n = 10 individual measurements).

The active substance content of the tablets was within the acceptance limits.

C L A I M S

1. A process for the preparation of pharmaceutical compositions for the oral application of bisphosphonates, wherein the bisphosphonate is wet-granulated in manner known per se in a fluidised-bed granulator using adjuvants which have no abrasive action and wherein the wet granulate is then dried in the fluidised bed, screened through a screen having a suitable mesh width and further processed by techniques known per se to form pharmaceutical compositions.

2. A process according to claim 1, wherein the bisphosphonate in solution or suspension and together with an aqueous binder is sprayed on to other adjuvants and granulated.

3. A process according to claim 1, wherein the bisphosphonate and the adjuvants in dry powder form are placed in a fluidised-bed reactor and granulated by the spraying of water into the powder mixture, which in that case contains a binder, or the powder containing the active substance is granulated by the spraying in of an aqueous binder solution.

4. A process according to any of claims 1 to 3, wherein the bisphosphonate used is alendronate, clodronate, EB-1053, etidronate, ibandronate, incadronate, neridronate, olpadronate, pamidronate, risedronate, tiludronate, YH 529 or zoledronate in the form of the free acid or a pharmaceutically compatible salt or hydrate, particularly the sodium salt.

e.g., colloidal silicon dioxide, tableting adjuvants etc. In one preferred embodiment the further processing of the granulate is carried out with the addition of stearic acid as lubricant in quantities of less than 5% by weight referred to the total weight of the form of administration, particularly 0.05 to 3% by weight of stearic acid.

Preparation of pharmaceutical compositions according to the invention by fluidised-bed granulation, particularly by the drying process in the fluidised-bed granulator, results in less intensive contact between the material and the surface of the apparatus, thus surprisingly reducing the loss of active substance. This is particularly advantageous when the active substance content of the unit dose is small. This substantially avoids the above-described disadvantages in the conventional production of forms for oral administration.

The invention will now be explained in further detail with reference to examples, without being limited thereto.

5. A process according to claim 4, wherein the bisphosphonate used is ibandronate.

6. A process according to any of claims 1 to 5, wherein at least one of the adjuvants is: lactose, microcrystalline cellulose or polyvinyl pyrrolidone.

7. A process according to claim 6, wherein the adjuvants used are 1-99% by weight lactose, 1-99% by weight microcrystalline cellulose and 0.1-20% polyvinyl pyrrolidone.

8. A process according to claim 7, wherein 25-75% by weight lactose, 10-20% by weight microcrystalline cellulose and 2-3% by weight polyvinyl pyrrolidone are used.

9. A process according to any of claims 1 to 8, wherein further processing into tablets, capsules, film tablets, dragees, pellets, effervescent tablets, chewing tablets or granulates in sachets is carried out.

10. A process according to claim 9, wherein further processing is effected with the addition of 0.05 - 3% by weight stearic acid to the mixture.

11. A process according to any of claims 1 to 10 for the preparation of forms of administration containing up to 50 mg active substance per unit dose.

12. Pharmaceutical compositions for the oral application of bisphosphonates when made according to any one of claims 1 to 11.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C.,

Abogado
ALICIA LLOREDA RICAURTE
Apoderado

ASUNTO	Radicación	04-096462
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	10374
	Folios	18

Patente de Invención ■ Patente de Modelo de Utilidad ☐

Vía Nacional ☐

Vía PCT (fase nacional) ■ Cap.I ☐ Cap. II ■

No. Sol. Internacional PCT/EP03/04629
Fecha de Presentación Internal. 02 de Mayo de 2003

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

1.1. Descripción: Folios: 61 a 103 como se radicó inicialmente
1.2. Reivindicaciones: Folios 18 a 20 como se radicó inicialmente
Folios 51 a 52 modificadas en fase nacional
Folios 109 a 110 modificadas en fase nacional
1.3. Prioridad: Folios: 1
10 de Mayo de 2002, EP, 02010136.6

1.4. Respuesta del solicitante: Folios: 93 a 123

2. Análisis de la Prioridad

- La fecha de prioridad del 10 de Mayo de 2002 y su correspondiente documento, corresponden con la materia solicitada de protección.

3. Objeto de la invención

- Título de la solicitud: **"ÁCIDO BIFOSFÓNICO PARA EL TRATAMIENTO Y PREVENCIÓN DE OSTEOPOROSIS"** Folio 1.

El objeto de la presente solicitud de patente de invención consiste en el empleo de los ácidos bifosfónicos o las sales farmacéuticamente aceptables de los mismos, especialmente el ácido ibandrónico para la prevención y tratamiento de la osteoporosis.

Reivindicación 1-6: Medicamento

El problema planteado en esta solicitud es la prevención o tratamiento de trastornos caracterizados por un aumento patológico de la resorción ósea.

Para solucionar este problema técnico la solicitud en estudio proporciona un medicamento de un ácido bifosfónicos o las sales farmacéuticamente aceptables de los mismos.

- **Clasificación Internacional de Patentes (IPC):** *A61K9/36; A61K9/20; A61K9/28; A61K31/662; A61K31/663; A61K47/04; A61K47/12; A61K47/26; A61K47/32; A61K47/34; A61K47/38; A61K9/30; A61K9/20; A61K47/02.*

4. De la solicitud de Patente

4.1. Descripción *(artículo 28 D. 486)*

- No se encontraron datos comparativos con las composiciones previamente divulgadas que presenten el efecto técnico inesperado alcanzado y sus ventajas superiores.
- No se encuentran sustentados ejemplos de las formulaciones del medicamento con 100 o 150mg de principio activo.

4.2. Reivindicaciones *(artículo 30 D 486)*

- La reivindicación 1 se encuentra enunciada por "administrado mensualmente" lo cual se refiere a un método de tratamiento.
- La reivindicación 6 se refiere al medicamento de forma general y amplia sin encontrarse plenamente caracterizado, sin encontrarse acorde con lo descrito en el ejemplo 1. (Ver folio 50)

5. Determinación del Estado de la Técnica

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es: 13/11/2000 se encontraron los siguientes documentos del estado de la técnica relacionados, que pueden afectar la patentabilidad del objeto de la presente solicitud:

N°	Documento	Título	Fecha de publicación
D1	US 6,143,326	"Oral pharmaceutical preparation containing ibandronat"	30/10/1997
D2	WO 00/21541	"Process for the preparation of oral pharmaceutical compositions comprising biphosphonates"	20/04/2000

6. Análisis de patentabilidad (artículo 14 D486)

6.1 Novedad (artículo 16 D486)

6.1.1. Solicitud presentada

La reivindicación 1 de la solicitud presentada se refiere a un **medicamento oral** caracterizado porque comprende **100mg** o **150mg** de un **ácido bifosfónico** o una sal farmacéuticamente aceptable del mismo y uno o más excipientes farmacéuticamente aceptables.
La reivindicación 2 se refiere al **ácido bifosfónico** como **ácido ibandrónico** o **una sal farmacéuticamente aceptable.**

D1 divulga preparaciones farmacéuticas orales que contienen **ibandronato o una sal tolerable fisiológicamente** como sustancia activa conteniendo una porción interior rodeada por una cubierta libre de sustancia activa de rápida liberación (Ver resumen)

La reivindicación 1 de **D1** se refiere a una formulación que comprende un núcleo de tableta que contiene entre 0.1 a 100mg de ibandronato y una cubierta la cual es libre de ibandronato (Ver columna 6, líneas 46-56)

D1 también se refiere a la cantidad de la sustancia activa de ibandroanto es empleada en cantidades de 0.1-100mg por unidad de dosificación única, **siendo el límite superior cerca de 250mg**, particularmente 100mg y 50mg respectivamente. (Ver columna 5, líneas 7-12)

Conforme a lo anteriormente descrito se concluye que **el medicamento oral** caracterizado porque comprende **100mg o 150mg** de un **ácido bifosfónico** o una sal farmacéuticamente aceptable del mismo y uno o más excipientes farmacéuticamente aceptables donde el **ácido bifosfónico** es **ácido ibandrónico** o **una sal farmacéuticamente aceptable** del mismo, en comprimidos recubiertos, no son novedosos.

6.1.2. Solicitud presentada

La reivindicación 5 se refiere a un medicamento que comprende un ácido bifosfónico o una sal farmacéuticamente aceptable del mismo, donde es la **sal monósódica de ácido ibandrónico, monohidrato**

La reivindicación 6 se refiere al medicamento, caracterizado porque es un **comprimido recubierto por una película**, donde **los excipientes son** seleccionados entre el grupo conformado por:

- Lactosa, polivinilpirrolidona, celulosa microcristalina, crospovidona, ácido esteárico y dióxido de silicio y
- Hidroxipropilmetilcelulosa, óxido de titanio, talco y polietilénglicol 6000

Anterioridades

D1 es el estado más cercano de la técnica pues divulga una formulación que comprende un núcleo de tableta que contiene entre **0.1 a 100mg de ibandronato** y una cubierta la cual es libre de ibandronato con la siguiente proporción: (Ver columna 6, líneas 46-56)

- **51.425%** por peso de **hidroxipropilmetilcelulosa**
- **24.650%** por peso de **dióxido de titanio**
- **15.000%** por peso de **polietilénglicol**
- **8.925%** por peso de **talco**

El ejemplo de la solicitud presentada utiliza en las tabletas de 50mg de ibandronato los mismos excipientes enunciados en **D1**, por lo tanto no se consideran novedosos

los comprimidos recubiertos donde se utilizan como excipientes: hidroxipropilmetilcelulosa, óxido de titanio, talco y polietilénglicol. (Ver folio 50):

D2 divulga previamente un proceso para la preparación de composiciones farmacéuticas orales que comprenden bifosfonatos. (Ver resumen)

El ibandronato es la sustancia activa preferida en **D2** particularmente en la forma de **monohidrato de ibandronato sódico** en una proporción hasta **50mg.** (Ver página 6, líneas 1-7)

El ejemplo 3 y 4 de **D2**, enseñan formulaciones para tabletas las cuales contienen **lactosa, polivinilpirrolidona, celulosa microcristalina, crospovidona, ácido esteárico y dióxido de silicio** (Ver página 10 y 11).

La reivindicación 7 enseña que los adyuvantes usados se encuentran en las proporciones de **lactosa en 1-99%** por peso, **polivinilpirrolidona en 0.1-20%** por peso, **celulosa microcristalina en 1-99%** por peso. (Ver página 14, líneas 8-11-**D2**)

La reivindicación 9 enseña que el proceso aplica a **tabletas recubiertas**. (Ver página 14, líneas 19-20-**D2**)

La reivindicación 10 se refiere al peso de **ácido esteárico** a la mezcla en una proporción de **0.05-3%** (Ver página 14, líneas 24-26-**D2**)

El solicitante en el ejemplo enseña los mismos componentes previamente divulgados para el núcleo de las tabletas tales como **lactosa** en 1-99% por peso, **polivinilpirrolidona** en 0.1-20% por peso, **celulosa microcristalina** en 1-99% por peso, crospovidona y dióxido de silicio (Ver folio 50), careciendo por lo tanto de novedad el uso de los excipientes anteriormente enunciados.

6.2 Nivel inventivo *(artículo18 D486)*

Es evidente para el experto en la materia que de acuerdo a lo previamente divulgado en **D1** y **D2,** se obtendría **el medicamento oral de ibandronato monosódico monohidrato en comprimidos recubiertos** de **100mg o 150mg,** utilizando los mismos excipientes antes enseñados tales como lactosa, polivinilpirrolidona, celulosa microcristalina, crospovidona, ácido esteárico y dióxido de silicio e hidroxipropilmetilcelulosa, óxido de titanio, talco y polietilénglicol.

El problema técnico planteado en esta solicitud como es obtener **"es la prevención o tratamiento de trastornos caracterizados por un aumento patológico de la resorción ósea",** sería solucionado fácilmente por el experto en la materia con base en las composiciones farmacéuticas divulgadas en **D1** y **D2**, de manera que este lo lograría fácil y obviamente sin necesidad de emplear Habilidad Inventiva.

Por lo tanto las reivindicaciones 4 a 6 carecen de nivel inventivo.

6. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

N°	Documento N°	Reivindicaciones afectadas	Requisito que afecta
D1	US 6,143,326	1-3	Novedad

			Nivel Inventivo
D2	**WO 00/21541**	**1-3**	**Novedad** **Nivel Inventivo**

7. Respuesta a los argumentos del solicitante:

- Los documentos anexados por el solicitante según folios 111 a 123 no evidencian, el empleo del medicamento del solicitante según las reivindicaciones 1 a 6.
  Los documentos se refieren al empleo de las dosis de 100mg o 150mg para su correspondiente administración única mensual como método de tratamiento, lo cual no es patentable de acuerdo a la legislación vigente colombiana. La cantidad de fármaco tal como 100mg o 150mg no es elemento característico único que define el medicamento en su conjunto y que permite una única administración mensual.
- De acuerdo con las observaciones del solicitante con respecto a la documentación allegada por Tecnoquímicas corresponde a **"remisión de información"**

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de 60 días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha _____

CONCEPTO TÉCNICO No. 01619	**EXAMINADOR TÉCNICO** Código No. 202070

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 04-096462- -00007-0000
Fecha 2008-11-07 16:20:08 Dep 2020 NUEVAS ACCIONES
Rad 11 PATENTES Liq 379 CLASE NACIONAL
Act 444 RESPUESTA RECURSO Folios 50

Señor
SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E. S. D.

Re: P1.- **F. HOFFMANN-LA ROCHE AG** -Solicitud de Patente de Invención en Fase Nacional PCT para "**ÁCIDO BISFOSFÓNICO PARA EL TRATAMIENTO Y PREVENCIÓN DE OSTEOPOROSIS**".-Clase **A61P 19/10**.-Expediente número **04-096.462.-**

1. Me refiero al auto dictado por ese Despacho notificado por fijación en lista el 15 de Agosto de 2008.

2. Con el fin de responder a las objeciones expuestas por el señor Examinador en su Concepto Técnico No. **1619** bajo los acápites de Claridad, Novedad y Nivel inventivo, atentamente me permito presentar los siguientes argumentos técnicos y las siguientes modificaciones hechas en el capítulo reivindicatorio de la solicitud en cuestión, mediante lo cual no sólo se superan dichas objeciones, sino que además se demuestra en forma contundente la patentabilidad de la presente invención.

3. **MODIFICACIONES A LA SOLICITUD**

Inicialmente me permito manifestar que el solicitante ha decidido alterar el capítulo reivindicatorio actualmente presentado, **modificando** la reivindicación 1 y **eliminando** la reivindicación 6. Por lo tanto, el nuevo capítulo reivindicatorio que se remite junto con el presente memorial está compuesto por cinco (5) reivindicaciones cuyo sustento se analiza a continuación:

- La *nueva reivindicación* 1 está dirigida a proteger un medicamento para administración oral caracterizado porque es un comprimido recubierto por una película, en donde el núcleo del comprimido comprende:

  - 100 mg o 150 mg de un ácido bisfosfónico o una sal farmcéuticamente aceptable del mismo; y

- uno o mas excipientes farmacéuticamente aceptables seleccionados del grupo conformado por: lactosa, polivinilpirrolidona, celulosa microcristalina, crospovidona, ácido esteárico y dióxido de silicio;

y en donde el recubrimiento del comprimido comprende uno o mas excipientes farmacéuticamente aceptables seleccionados entre el grupo conformado por: hidroxipropil metilcelulosa, dióxido de titanio, talco y polietilenglicol 6000.

Dicha nueva reivindicación 1 presenta adecuado sustento, por ejemplo, en la página 14 (líneas 2 a 24) de la descripción.

Ahora bien, en este punto resulta de gran importancia mencionar que en la página 8 (línea 15) del texto correspondiente a la publicación internacional de la presente solicitud (documento WO 03/095029), así como en la página 14 (líneas 20 y 21) de la descripción presentada en fase nacional, se hace referencia a la composición del núcleo del comprimido, hecho que constituye un evidente error involuntario debido a que el núcleo del comprimido no está compuesto por uno o más excipientes farmacéuticamente aceptables seleccionados entre hidroxipropil metilcelulosa, dióxido de titanio, talco y polietilenglicol 6000, sino que está compuesto por uno o más excipientes farmacéuticamente aceptables seleccionados entre lactosa, polivinilpirrolidona, celulosa microcristalina, crospovidona, ácido esteárico y dióxido de silicio, tal como se encuentra definido en las líneas 11 a 15 de la página 8 y en la Tabla 1 (página 10) del documento WO 03/095029.

En este sentido, dicho error ha sido corregido dentro del texto de la descripción presentada en fase nacional, mediante el reemplazo del término "núcleo" por el término correcto "recubrimiento" en la página 14 (línea 20) de dicho documento (anexo iii).

- Por su parte, las reivindicaciones 2 a 5 actualmente presentadas no han sido modificadas.

En vista de lo anterior, me permito resaltar que las modificaciones realizadas al capítulo reivindicatorio de la presente solicitud **no amplían de manera alguna el alcance establecido en la memoria descriptiva originalmente presentada**, cumpliendo a cabalidad con los requisitos de patentabilidad estipulados en el Artículo 34 de la Decisión 486 de 2000.

4. CLARIDAD DE LA SOLICITUD

El señor Examinador ha objetado la claridad de la presente solicitud con base en los siguientes argumentos:

Descripción

- ***"No se encontraron datos comparativos con las composiciones previamente divulgadas que demuestren su aporte al estado de la técnica, y el efecto inesperado alcanzado"***

Frente a este particular, inicialmente me permito mencionar que el señor Examinador argumenta en su Concepto Técnico que los documentos remitidos a ese Despacho junto con la respuesta dada al Artículo 45 notificado el 14 de marzo de 2008 y respondido el 13 de junio de 2008, *"no evidencian el empleo del medicamento del solicitante según las reivindicaciones 1 a 6".*

En vista de lo anterior, me permito presentar ante ese Despacho un compendio actualmente publicado en internet *(www.emc.medicines.org.uk)* de las principales características fisicoquímicas y farmacológicas del medicamento revelado en la presente solicitud, es decir, del comprimido recubierto con una película que comprende 150 mg de ácido ibandrónico (ANEXO IV). En dicho documento se describe no solamente la composición cualitativa y cuantitativa de dicho medicamento *(composición que efectivamente corresponde a lo definido en la nueva reivindicación 1 de la invención en cuestión),* sino que también se revela un resumen de los principales resultados experimentales obtenidos por el solicitante en relación con la actividad farmacológica del medicamento, los cuales, por ejemplo, demuestran inequívocamente las sorprendentes ventajas técnicas logradas mediante la utilización de un comprimido que contenga 150 mg de ácido ibandrónico en el tratamiento de la resorción ósea, frente a la utilización de un comprimido que contenga 2,5 mg de dicho compuesto activo, y que era conocido en el estado de la técnica anterior (numeral 5 del anexo IV).

En consecuencia, me permito manifestar que los documentos técnicos remitidos a ese Despacho junto con el pasado memorial y junto con el presente escrito, sustentan de manera inequívoca el sorprendente aporte al estado de la técnica logrado por el solicitante a través de la información técnica revelada en la invención en cuestión.

- ***"No se encuentran sustentados ejemplos de las formulaciones del medicamento con 100 o 150 mg de principio activo"***

En respuesta a lo anterior, inicialmente resulta de gran importancia resaltar que si bien el ejemplo 1 presentado en la descripción de la solicitud (página 17) hace referencia a un comprimido que contiene 50 mg de ácido ibandrónico (equivalentes a 56.250 mg de la sal monosódica del ácido ibandrónico monohidrato) en combinación con una serie de excipientes que conforman tanto el núcleo como el recubrimiento de dicho comprimido, **a lo largo de la**

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descripción también se hace referencia explícita a un medicamento que contiene preferiblemente entre 100 y 150 mg de ácido ibandrónico o una sal farmacéuticamente aceptable del mismo [ver, por ejemplo, las páginas 6 (líneas 14 a 17), 7 (líneas 23 a 25) y 10 (líneas 3 a 6)]. En este sentido, es claro que la presente solicitud sí menciona un medicamento que comprende 100 ó 150 mg de principio activo.

Teniendo en cuenta lo anterior, me permito nuevamente resaltar ante ese Despacho la información técnica revelada en el anexo IV del presente escrito, toda vez que allí se describen plenamente la composición y las características fisicoquímicas y farmacológicas del medicamento revelado en la presente solicitud y que es mundialmente conocido bajo el nombre de BONVIVA, esto es, **se describe completamente un comprimido recubierto por una película, cuyo núcleo contiene 150 mg de ácido ibandrónico mezclado con lactosa, povidona, celulosa microcristalina, crospovidona, ácido esteárico y óxido de silicio, y cuyo recubrimiento está conformado por dióxido de titanio, talco, hipromelosa y magrocol 6000.**

En este sentido, atentamente considero que la información aportada por el solicitante ejemplifica de manera clara y concisa la composición y las características fisicoquímicas y farmacológicas del medicamento revelado en la presente invención, con lo cual se supera completamente la objeción realizada por el señor Examinador a éste respecto.

Reivindicaciones

- ***"La reivindicación 1 se encuentra enunciada por administrado mensualmente" lo cual se refiere a un método de tratamiento"***

Atendiendo a lo anterior, y tal como se mencionó en el numeral 3 del presente memorial, me permito manifestar que el solicitante ha decidido **eliminar** la expresión ***"administrado mensualmente"*** de la reivindicación 1, con lo cual se supera satisfactoriamente la objeción realizada por el señor Examinador a éste respecto.

- ***"La reivindicación 6 se refiere al medicamento de forma general y amplia sin encontrarse plenamente caracterizado, sin encontrarse acorde con lo descrito en el ejemplo 1"***

En respuesta a lo anterior, me permito manifestar que el solicitante ha decidido **eliminar la reivindicación 6 actualmente presentada**, con lo cual se supera completamente la objeción realizada por el señor Examinador a este respecto.

Finalmente, en vista de los argumentos técnicos planteados hasta el momento, y de conformidad con las modificaciones realizadas a la solicitud en cuestión, me permito manifestar que la presente invención cumple a cabalidad con los requisitos de patentabilidad establecidos en los Artículos 28 y 30 de la Decisión 486 de 2000.

5. ANÁLISIS DE LA NOVEDAD Y DEL NIVEL INVENTIVO

De otro lado, el señor Examinador ha objetado la novedad y el nivel inventivo de la presente solicitud con base en las enseñanzas de los siguientes documentos:

- US 6,143,326 **(D1)**
- WO 00/21541 **(D2)**

En este sentido, el señor Examinador argumenta básicamente que en el documento D1 se enseña una formulación que comprende un núcleo de tableta que contiene entre 0.1 a 100 mg de ibandronato y una cubierta libre de ibandronato.

Asimismo, el señor Examinador argumenta que el documento D2 divulga un proceso para la preparación de composiciones farmacéuticas orales que comprenden bisfosfonatos, siendo el ibandronato la sustancia activa preferida, particularmente en una proporción hasta de 50 mg. En este sentido, el señor Examinador también afirma que en los ejemplos 3 y 4 de dicha anterioridad se enseñan formulaciones para tabletas que contienen lactosa, polivinilpirrolidona, celulosa microcristalina, crospovidona, ácido esteárico y dióxido de silicio.

Debido a lo anterior, el señor Examinador concluye que la información técnica revelada en la presente solicitud no es novedosa frente a las enseñanzas de los documentos D1 y D2.

De otro lado, el señor Examinador afirma que para una persona experta en la materia que se base en las enseñanzas de los documentos D1 y D2 sería evidente obtener el medicamento oral de ibandronato monosódico monohidrato en comprimidos recubiertos de 100 mg o 150 mg con los mismos excipientes enseñados en tales anterioridades, por lo que concluye que el problema técnico planteado en la presente solicitud sería resuelto fácilmente por el experto en la materia sin necesidad de emplear habilidad inventiva.

Ahora bien, para responder adecuadamente a dichas objeciones, inicialmente me permito realizar un resumen de las principales enseñanzas de cada una de dichas anterioridades, así como un análisis comparativo detallado entre tales enseñanzas y la materia revelada en la presente solicitud.

5.1 **Consideraciones con respecto al documento US 6'143,326 (D1)**

En términos generales, el documento D1 enseña composiciones farmacéuticas para aplicación oral que contienen ibandronato o una sal fisiológicamente tolerable del mismo.

Específicamente, y de acuerdo con lo establecido por los autores de dicho documento, las formulaciones sólidas enseñadas en D1 comprenden: a) un núcleo que contiene entre 0.1 mg y 100 mg de ibandronato; y, b) un recubrimiento conformado por hidroxipropilmetilcelulosa, polietilenglicol, dióxido de titanio y talco, es decir, un recubrimiento que está libre de ingrediente activo pero que se caracteriza por permitir que éste último sea liberado rápidamente.

5.1.1 **Análisis de la novedad frente a D1**

Con base en lo anterior y con el ánimo de demostrar el inequívoco carácter novedoso que presenta la información técnica revelada en la presente solicitud frente a las enseñanzas del documento D1, a continuación me permito presentar ante ese Despacho las siguientes consideraciones técnicas:

- En primer lugar, resulta de gran importancia mencionar una vez más que de acuerdo con las modificaciones realizadas en el capítulo reivindicatorio de la invención en cuestión (numeral 3 del presente memorial), esta solicitud se encuentra dirigida a proteger un medicamento para administración oral caracterizado porque es un comprimido recubierto por una película, en donde el núcleo del comprimido comprende:

  - 100 mg o 150 mg de un ácido bisfosfónico o una sal farmcéuticamente aceptable del mismo; y

  - uno o mas excipientes farmacéuticamente aceptables seleccionados del grupo conformado por: lactosa, polivinilpirrolidona, celulosa microcristalina, crospovidona, ácido esteárico y dióxido de silicio;

  y en donde el recubrimiento del comprimido comprende uno o más excipientes farmacéuticamente aceptables seleccionados entre el grupo conformado por: hidroxipropil metilcelulosa, dióxido de titanio, talco y polietilenglicol 6000.

- Por su parte, de la atenta lectura del documento D1 es claro que dicha anterioridad enseña, por ejemplo, formulaciones farmacéuticas conformadas por:

  a) un núcleo de tableta que comprende entre 0.1 mg y 100 mg de ibandronato; y

b) un recubrimiento libre de ibandronato que presenta la siguiente composición:

a. alrededor de 51.425% en peso de hidroxipropilmetilcelulosa,
b. alrededor de 24.650% en peso de dióxido de titanio,
c. alrededor de 15.000% en peso de polietilenglicol, y
d. alrededor de 8.925% en peso de talco

Asimismo, tanto en las columnas 3 y 4, como en los ejemplos 1, 2, 3, 4 y 7 del documento D1 se mencionan otros polímeros y adyuvantes que pueden hacer parte del recubrimiento de las formulaciones farmacéuticas allí reveladas. **Sin embargo, es de gran importancia resaltar que a lo largo de dicha anterioridad se enseña claramente que el compuesto activo (ibandronato) NO está mezclado con excipientes o adyuvantes.**

- Ahora bien, de conformidad con lo mencionado en los dos puntos anteriores, es absolutamente claro que el documento D1 **NO** enseña un **comprimido cuyo núcleo está conformado por la mezcla de:**
  - 100 mg ó 150 mg de un ácido bisfosfónico (o una sal farmacéuticamente aceptable del mismo), y
  - uno o más excipientes farmacéuticamente aceptables seleccionados del grupo conformado por: lactosa, polivinilpirrolidona, celulosa microcristalina, crospovidona, ácido esteárico y dióxido de silicio;

  y cuyo recubrimiento esté conformado por uno o más excipientes farmacéuticamente aceptables seleccionados entre el grupo conformado por: hidroxipropil metilcelulosa, dióxido de titanio, talco y polietilenglicol 6000.

Por lo tanto, me permito manifestar que la información técnica revelada en la invención en cuestión presenta un **inequívoco carácter novedoso frente a las enseñanzas del documento D1,** esto es, cumple a cabalidad con las disposiciones de patentabilidad requeridas en el Artículo 16 de la Decisión 486 de 2000.

5.2 Consideraciones con respecto al documento WO 00/21541 (D2)

El documento D2 enseña un proceso para la preparación de composiciones farmacéuticas que contienen bisfosfonatos, el cual está caracterizado básicamente porque la sustancia activa es inicialmente granulada en húmedo por medio de un granulador de lecho fluidizado junto con adyuvantes que no presentan acción abrasiva, y posteriormente es secada, tamizada y procesada para obtener las composiciones farmacéuticas requeridas.

En conexión con lo anterior, resulta de gran importancia resaltar que el objetivo principal de dicha anterioridad era desarrollar un proceso que permitiera reducir las pérdidas de sustancia activa durante el proceso de preparación de composiciones farmacéuticas que contienen no más de 50 mg de bisfosfonatos por unidad de dosis.

5.2.1 **Análisis de la novedad frente a D2**

Con base en lo anterior y con el ánimo de demostrar el inequívoco carácter novedoso que presenta la información técnica revelada en la presente solicitud frente a las enseñanzas del documento D2, inicialmente me permito manifestar que dicha anterioridad no enseña un comprimido cuyo núcleo está conformado por la mezcla de:

- 100 mg ó 150 mg de un ácido bisfosfónico (o una sal farmacéuticamente aceptable del mismo), y

- uno o más excipientes farmacéuticamente aceptables seleccionados del grupo conformado por: lactosa, polivinilpirrolidona, celulosa microcristalina, crospovidona, ácido esteárico y dióxido de silicio;

y cuyo recubrimiento esté conformado por uno o más excipientes farmacéuticamente aceptables seleccionados entre el grupo conformado por: hidroxipropil metilcelulosa, dióxido de titanio, talco y polietilenglicol 6000.

Contrario a esto, el documento D2 únicamente revela un proceso para obtener composiciones farmacéuticas caracterizadas porque comprenden un bajo contenido de ingrediente activo, específicamente, para composiciones farmacéuticas que comprenden hasta 50 mg de ibandronato.

Ahora, teniendo en cuenta los lineamientos establecidos en el Manual Andino de Patentes para llevar a cabo el análisis de la novedad de una solicitud, es claro que un documento puede afectar la novedad de una invención solo si éste contiene explícitamente todas las características técnicas esenciales de la invención bajo estudio, esto es, si dicha anterioridad describe por sí sola todas las características técnicas contenidas en las reivindicaciones analizadas.[1]

Por lo tanto, debido a que dichos requisitos no se cumplen en el presente caso, es claro que **el capítulo reivindicatorio de la presente solicitud de patente es novedoso frente a las enseñanzas del documento D2.**

[1] SECRETARÍA GENERAL DE LA COMUNIDAD ANDINA. Manual para el examen de solicitudes de patentes de invención en las Oficinas de Propiedad Industrial de los Países de la Cumunidad Andina. Lima, Perú; 2004; páginas 65 y 66.

5.3 **Análisis del nivel inventivo de la presente solicitud frente a los documentos D1 y D2**

De otro lado, para demostrar el nivel inventivo que caracteriza a la materia técnica revelada en la presente solicitud frente a las enseñanzas de los documentos D1 y D2, me permito dirigir la atención del señor Examinador hacia las enseñanzas del ANEXO IV remitido a ese Despacho junto con el presente memorial, toda vez que en dicho documento se presentan los datos experimentales que demuestran el sorprendente efecto técnico logrado con los medicamentos revelados en la presente invención durante el tratamiento de la resorción ósea.

Específicamente, tanto en dicho compendio (ANEXO IV) como en los documentos remitidos a ese Despacho junto con la respuesta dada al Concepto Técnico anterior, se revelan, -por ejemplo-, los resultados de un estudio realizado por el solicitante y que es conocido bajo el nombre de MOBILE (Monthly Oral iBandronate In LadiEs); dicho estudio consistió básicamente de la realización de un ensayo clínico durante dos años, aleatorizado y doble ciego con 1.609 mujeres con osteoporosis postmenopáusica, con el cual se comparó la eficacia y seguridad de diferentes dosis mensuales orales de ibandronato (100mg en un solo día; 100mg separados en dosis de 50mg durante dos días consecutivos o 150mg en un solo día) con el régimen diario oral (2.5mg) aprobado actualmente por la FDA y la Unión Europea.

Dicho estudio permitió concluir que la gran mayoría de mujeres cuyo régimen de tratamiento contra la resorción ósea consistió en el consumo mensual de un comprimido con 100 mg o 150 mg de ibandronato lograron incrementos significativos en la densidad mineral ósea tanto en la espina lumbar (LS BMD), como en la cadera (HT BMD). Así, por ejemplo, de acuerdo a los datos revelados en los documentos previamente mencionados, es claro que un 91.3% de pacientes a las que se les administró mensualmente 150 mg de ibandronato mostraron un aumento en la densidad mineral ósea de la espina lumbar (LS BMD), mientras que sólo un 84% de pacientes a quienes se les administró diariamente 2.5 mg de ibandronato mostraron un aumento en LS BMD. Asimismo, un mayor porcentaje de pacientes a las que se les administró mensualmente 100 mg (87.1%) y 150 mg (90.0%) de ibandronato lograron aumentos substanciales en la densidad mineral ósea en la cadera (TH BMD), pues sólo un 76.7% de pacientes a las que se les administró diariamente 2.5 mg de ibandronato lograron incrementos similares en TH BMD.

Aparte de lo anterior, el medicamento revelado en la presente solicitud también representa un importante avance en el estado de la técnica si se tiene en cuenta que para la gran mayoría de los pacientes el consumo diario de un medicamento que contiene 2,5 mg de ácido ibandrónico resulta inconveniente, lo que ocasionaba que hasta dos tercios de las pacientes abandonaran el tratamiento de la osteoporosis luego de un año, quedándose sin

los beneficios de la reconstrucción del hueso que estos fármacos sólo pueden proporcionar al cabo del tiempo.

Por todo lo anterior, atentamente me permito manifestar ante ese Despacho que el novedoso medicamento revelado en la solicitud de patente en cuestión presenta un inequívoco carácter inventivo frente a las enseñanzas de los documentos D1 y D2, toda vez **que una persona experta en la materia técnica en cuestión no encuentra en dichas anterioridades enseñanza alguna que le sugiera un medicamento de administración mensual que comprenda 100 ó 150 mg de ibandronato (o una sal farmacéuticamente aceptable del mismo) junto con excipientes farmacéuticamente aceptables**. Asimismo, es claro que la persona experta en la materia tampoco encontraría obvio el medicamento de la solicitud de patente en cuestión, debido a que éste no habría podido sugerir las notables ventajas técnicas y terapéuticas obtenidas a partir de dicha novedosa composición, tal como se ha comentado previamente en el presente memorial.

6. CONCLUSIÓN

Teniendo en cuenta las modificaciones realizadas en la descripción y en el capítulo reivindicatorio de la presente solicitud, y de conformidad con los argumentos técnicos presentados para demostrar el inequívoco carácter novedoso e inventivo de dicho nuevo capítulo reivindicatorio frente a las enseñanzas de los documentos D1 y D2, es completamente claro que se han superado todas las objeciones expuestas por el señor Examinador en contra de la patentabilidad de la presente invención, y por lo tanto, dicha solicitud es merecedora del privilegio de patente solicitado.

7. Anexo al presente memorial me permito presentar:

i) Recibo número 08-84,532, expedido por la Superintendencia de Industria y Comercio, que acredita el pago de las modificaciones mencionadas;

ii) Copia de las páginas 1-17 de la descripción, en la cual se ha realizado la modificación previamente mencionada;

iii) Copia del nuevo capítulo reivindicatorio compuesto por 5 reivindicaciones, el cual reemplaza al capítulo actualmente presentado y en el que se han realizado las modificaciones previamente mencionadas; y

iv) Copia del compendio electrónico para el medicamento denominado: *"Bonviva 150 mg Film-Coated Tablets".*

8. En vista de todo lo anterior, ruego a usted proceder a estudiar nuevamente la solicitud a la luz de las argumentaciones presentadas y de las modificaciones realizadas y conceder el privilegio de patente solicitado.

Señor Superintendente,

ALICIA LLOREDA RICAURTE

T.P. 53.215

NOTARIA SEXTA BOGOTA, D.C.

CODEX JURIS CIVILIS

NOTARIA SEXTA DE BOGOTA

RECONOCIMIENTO Y PRESENTACION PERSONAL

Bogotá, D.C. 04 NOV 2008

Ante mi AMPARO QUINTERO ARTURO,

NOTARIA SEXTA DEL CIRCULO DE

BOGOTA D.C.

Compareció(eron) Alicia Lloreda Ricaurte

Quien(es) exhibió(eron) la(s) C.C.

y declaró(aron) que la(s) firma(s) que aparece(n) en el presente documento es(son) la(s) suya(s) y que el contenido del mismo es cierto.

En constancia se firma esta diligencia.

ALICIA LLOREDA RICAURTE

C.C. No. 39.690.713 de Usaquén

REPUBLICA DE COLOMBIA

Amparo Quintero Arturo

NOTARIA

NOTARIA SEXTA DE BOGOTA

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 84,532
FECHA : OCTUBRE 27 DE 2008

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
LLOREDA Y CIA S. A	CONSIGNACION	BANCO DE BOGOTA	062754387	80211740	27/10/2008	9,353,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-03 CAMBIO DE MODALIDAD Y MODIFICA	12 MARCAS Y LEMAS COMERCIALES	103,000.00
		TOTAL : $	103,000.00

SON: CIENTO TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

F. Hoffmann la Roche AG

Exp. 04-096.462 153

ACIDO BISFOSFONICO PARA EL TRATAMIENTO Y PREVENCION DE OSTEOPOROSIS

RESUMEN-OBJETO Y FINALIDAD DE LA INVENCION

La presente invención se refiere al empleo de los ácidos bisfosfönicos o las sales farmacéuticamente aceptables de los mismos, para la elaboración de medicamentos para la prevención o tratamiento de transtornos caracterizados por un aumento patológico de la resorción ósea, especialmente para la prevención y tratamiento de la osteoporosis.

*****

ACIDO BISFOSFONICO PARA EL TRATAMIENTO Y PREVENCION DE OSTEOPOROSIS

La presente invención se refiere al empleo de los ácidos bisfosfónicos, especialmente del ácido (1-hidroxi-3-(N-metil-N-pentil)aminopropiliden-1,1,bisfosfónico (ácido ibandrónico) o las sales farmacéuticamente aceptables de los mismos, para la elaboración de medicamentos para la prevención o tratamiento de transtornos caracterizados por un aumento patológico de la resorción ósea, especialmente para la prevención y tratamiento de la osteoporosis.

Los huesos sirven principalmente como de soporte, y en consecuencia el hueso es contemplado con frecuencia como un simple material de construcción. Sin embargo, el hueso es un complicado biomaterial adaptado para una amplia variedad de necesidades, estímulos y agentes nocivos a los cuales está expuesto. Se dispone de endoprótesis como substitutos de huesos y articulaciones. Sin embargo, las endoprótesis aún cuando biomecánicamente son altamente refinadas, no tienen un efecto activo sobre el entorno ni en factores de carga.

Una variedad de transtornos en humanos y mamíferos implican o están asociados con la anormal resorción ósea. Estos desórdenes incluyen aunque no están limitados por ellas, la osteoporosis, la enfermedad de Paget, la pérdida periprostética de hueso u osteolisis, y la hipercalcemia de la enfermedad maligna y metastásica de los huesos. La más común de estas enfermedades es la osteoporosis, la cual en su manifestación más frecuente tiene lugar en las mujeres postmenopáusicas. Debido a que la osteoporosis así como otros transtornos asociados con la pérdida ósea, son condiciones

crónicas, se cree que la terapia adecuada requerirá generalmente un tratamiento crónico.

Los bisfosfonatos, a saber, los ácidos bisfosfónicos o las sales farmacéuticamente aceptables de los mismos, son compuestos sintéticos análogos del pirofosfato, que se encuentra en estado natural. Debido a su acusada afinidad para el fosfato de calcio en fase sólida, los bisfosfonatos se unen fuertemente al mineral del hueso. Los bisfosfonatos farmacológicamente activos son ya bien conocidos en la técnica y son potentes inhibidores de la resorción ósea y son por lo tanto de utilidad en el tratamiento y prevención de enfermedades que implican una resorción ósea anormal, especialmente la osteoporosis, la enfermedad de Paget, la hipercalcemia de malignidades y enfermedades metastásicas y metabólicas de los huesos.

Los bisfosfonatos como agentes farmacéuticos están descritos por ejemplo en las patentes EP-A-170.228, EP-A-197.478, EP-A-22.751, EP-A-252.504, EP-A-252.505, EP-A-258.618, EP-A-350.002, EP-A-273.190, WO-A-90/00798, etc., cada una de las cuales está incorporada a la presente como referencia.

Las formas farmacéuticas de los bisfosfonatos que se encuentran corrientemente en el mercado son formulaciones orales (comprimidos o cápsulas) o soluciones para la inyección o infusión intravenosa. Son sistémicamente bien tolerados cuando se administran a dosis terapéuticas. Sin embargo, los bisfosfonatos en su conjunto son irritantes para la piel y membranas mucosas, y cuando se añaden por vía oral

sobre una base continuada, pueden ocasionar efectos secundarios en el tracto digestivo, p. ej., episodios adversos o transtornos gastrointestinales. En consecuencia y debido a su baja biodisponibilidad oral, la ruta oral de administración ha sido hasta la fecha poco recomendada para emplear en pacientes.

Los bisfosfonatos pueden clasificarse en dos grupos con diferentes modos de acción. El ibandronato pertenece a los bisfosfonatos más potentes que contienen nitrógeno [Russell 1999 Russell RGG, Rogers ML]. Bisphosphonates: From the laboratory to the clinic and back again" ("Bisfosfonatos: Del laboratorio a la clínica y regreso"). Bone ("Hueso") 25 (1): 97-106 (1999); Rogers MJ, Gordon S, Benford HL, Coxon FP, Luckman SP, Monkkonen J, Frith JC. "Cellular Molecular mechanisms of action of bisphosphonates" ("Mecanismos moleculares celulares de acción de los bisfosfonatos"). Cancer ("Cáncer") 88 (12) Suppl: 2961-2978 (2000)]. El ibandronato es uno de los bisfosfonatos más potentes actualmente en desarrollo clínico en la osteoporosis y enfermedades metastásicas de los huesos. En modelos animales de resorción ósea, el ibandronato es 2, 10, 50 y 500 veces más potente que el risedronato, alendronato, pamidronato y clodronato respectivamente [Mühlbauer R.C.,F. Bauss, R. Schenk, M. Janner, E. Bosies, K. Strein y H. Fleisch. "BM 21.0955 a potent new bisphosphonate to inhibit bone resorption" ("BM 21.0955, un potente nuevo bisfosfonato para la inhibición de la resorción ósea"). J. Bone Miner. Res. 6: 1003 - 1001 (1991)].

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El ibandronato inhibe la resorción ósea sin perjudicar la mineralización (Mühlbauer y col., Mühlbauer R.C., F. Bauss, R. Schenk, M. Janner, E. Bosies, K. Strein, y H. Fleisch. "BM 21.0955 a potent new bisphosphonate to inhibit bone resorption" ("BM 21.0955, un potente nuevo bisfosfonato para la inhibición de la resorción ósea"). J. Bone Miner. Res. 6: 1003 - 1011 (1991).). Se ha demostrado que disminuye la actividad osteoclástica con lo cual inhibe la destrucción de los huesos. A dosis altas reduce también el número de osteoclastos (Mühlbauer y col., Mühlbauer R.C., F. Bauss, R. Schenk, M. Janner, E. Bosies, K. Strein y H. Fleisch. "BM 21.0955 a potent new bisphosphonate to inhibit bone resorption" ("BM 21.0955, un potente nuevo bisfosfonato para la inhibición de la resorción ósea"). J. Bone Miner. Res. 6: 1003 - 1011 (1991)).

Como se ha descrito, los bisfosfonatos son aceptados por proporcionar una fuerte eficacia en el control de la osteoporosis. Sin embargo, dadas las restricciones de administración relacionadas con la baja biodisponibilidad oral y potenciales efectos gastro intestinales, existe una clara oportunidad para los regímenes que ofrecen una mejor comodidad y flexibilidad, conduciendo a un nivel más alto de aceptación y un superior control/satisfacción del paciente. Se han descrito en la técnica regímenes intermitentes como por ejemplo, la administración una vez a la semana, pero dichos tratamientos intermitentes no proporcionan el resultado deseado.

Se ha descubierto ahora que la prevención o el

tratamiento de transtornos caracterizados por un aumento patológico de la resorción ósea como p. ej., la osteoporosis, pueden ser mejorados mediante la administración mensual de 50 a 250 mg de un bisfosfonato o una sal farmacéuticamente aceptable del mismo, especialmente mediante una administración mensual de ibandronato, es decir, ácido ibandrónico o una sal farmacéuticamente aceptable del mismo.

La presente invención se refiere por lo tanto al empleo de un ácido bisfosfónico o una sal farmacéuticamente aceptable del mismo, particularmente con el empleo del ácido ibandrónico o una sal farmacéuticamente aceptable del mismo, para la preparación de medicamentos para la prevención o tratamiento de trastornos caracterizados por un aumento patológico de la resorción ósea, en donde el medicamento:

a) contiene aproximadamente de 50 a 250 mg, de preferencia aproximadamente 100 a 150 mg de un ácido bisfosfónico o una sal farmacéuticamente aceptable del mismo, y

b) el medicamento se administra por vía oral en uno, dos o tres días consecutivos por mes.

El tratamiento por vía oral mensual, mediante la administración de por lo menos el 120%, especialmente del 120% al 200% de la dosis prevista, ofrece mayores ventajas para el paciente con respecto a la comodidad y aceptación así como superiores resultados. La "dosis prevista" (100%) corresponde a las dosis diarias eficaces acumuladas. Antes de completar el programa de desarrollo clínico del ibandronato, ningún bisfosfonato había demostrado prospectivamente una

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eficacia en la reducción de fracturas con un intervalo sin fármaco, fuera de la administración diaria. En resumen, es completamente inesperado que el beneficio de la reducción de fracturas pueda derivarse de una administración mensual de un bisfosfonato con un esquema de administración de un comprimido único o de varios comprimidos.

En consecuencia, la presente invención se refiere al empleo de ácidos bisfosfónicos o sales farmacéuticamente aceptables de los mismos para la elaboración de un medicamento para la prevención o tratamiento de transtornos caracterizados por un aumento patológico de la resorción ósea, p. ej., la osteoporosis, en donde el medicamento contiene por lo menos el 120% de la dosis diaria eficaz prevista, de ácidos bisfosfónicos o sales farmacéuticamente aceptables de los mismos, y se administra en uno, dos o tres días consecutivos por mes.

Con más preferencia, la invención comprende el empleo del ácido ibandrónico o las sales farmacéuticamente aceptables del mismo, para la elaboración de un medicamento para la prevención o tratamiento de transtornos caracterizados por un aumento patológico de la resorción ósea en donde el medicamento,

a) contiene aproximadamente de 100 a aproximadamente 150 mg de ácido ibandrónico o una sal farmacéuticamente aceptable del mismo, y

b) se administra por vía oral en uno, dos o tres días consecutivos por mes.

El término "ácido bisfosfónico" significa compuestos

caracterizados por dos grupos fosfónicos unidos por enlaces fosfoéter a un átomo de carbono central (geminal). Esta estructura P-C-P está ejemplificada en la fórmula I de más adelante. Debe tenerse en cuenta que el término "ácidos bisfosfónicos" como se emplea en la presente cuando se refiere a los agentes terapéuticos de la presente invención, se emplea también para abarcar los bisfosfonatos, los ácidos bifosfónicos y los ácidos bisfosfónicos, así como también las sales y derivados de estos materiales. El empleo de una nomenclatura específica al referirse al bisfosfonato o bisfosfonatos no significa que se limita el ámbito de la presente invención, a no ser que esté específicamente indicado.

El término "farmacéuticamente aceptable" como se emplea en la presente, significa que las sales o agentes quelantes son aceptables desde el punto de vista de la toxicidad.

El término "sal farmacéuticamente aceptable", se refiere a las sales de amonio, sales de metal alcalino tales como potasio y sodio (incluyendo las sales mono, di y trisódicas que son las preferidas), sales de metal alcalinotérreo tales como las sales de calcio y de magnesio, con bases orgánicas, como p. ej., las sales de diciclohexilamina, N-metil-D-glucamina y sales con aminoácidos tales como la arginina, lisina, etc.

El término "transtornos caracterizados por un aumento patológico de la resorción ósea" se refiere a las condiciones definidas médicamente con o sin causa identificable (tal como una osteoporosis menopáusica, osteoporosis

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juvenil idiopática, osteoporosis asociada con el síndrome de Klinefelter, osteoporosis masculina, osteoporosis debido a factores nutricionales, osteoporosis relacionada con el trasplante de un órgano, osteoporosis asociada con la inmovilización, condición inflamatoria y la osteoporosis inducida por corticosteroides).

El término "uno, dos o tres días consecutivos por mes" significa la administración de comprimidos proporcionales de una a tres dosis, o no proporcionales a ninguna dosis, en uno, dos o tres días consecutivos del mes, de preferencia un día por mes. Como se emplea en la presente, el término "mes" se emplea de acuerdo con el significado generalmente empleado de una medida del tiempo que comprende aproximadamente cuatro (4) semanas, aproximadamente 30 días, o aproximadamente 1/12 de un año natural.

El término "medicamento" se refiere a una composición farmacéutica. El término abarca los esquemas de administración simple o múltiple.

De preferencia el medicamento se administra una vez al mes. De preferencia el medicamento se administra como dosis única, aunque el ámbito de la presente invención incluye medicamentos administrados como subdosis múltiples como p. ej., en dos días consecutivos por mes o tres días consecutivos por mes.

De preferencia, el medicamento comprende por lo menos el 100%, de preferencia del 120% al 200%, con más preferencia del 120 al 150% de la dosis eficaz de ácidos bisfosfónicos o sales farmacéuticamente aceptables de los mismos, con más

preferencia del ácido ibandrónico o sales farmacéuticamente aceptables del mismo. 162

El término "dosis eficaz" se refiere aproximadamente de 50 a aproximadamente 250 mg, con más preferencia de aproximadamente 100 a aproximadamente 150, de un bisfosfonato o sales farmacéuticamente aceptables del mismo, por ejemplo de ácido ibandrónico o una sal farmacéuticamente aceptable del mismo. Como se ha indicado, la dosis eficaz puede ser una dosis simple o múltiples subdosis. Por ejemplo si la dosis eficaz es de 150 mg, la dosis puede ser una (1) dosis de 150 mg, dos (2) subdosis de 75 mg administradas en un día o en dos días consecutivos, o tres (3) subdosis de 50 mg administradas en un día o en dos o tres días consecutivos, si la dosis eficaz es de 100 mg, la dosis puede incluir una (1) dosis de 100 mg, dos (2) subdosis de 50 mg administradas en un día o dos días consecutivos, de preferencia en dos días consecutivos.

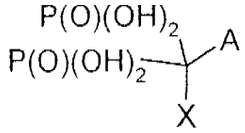
"Acidos bisfosfónicos y sales farmacéuticamente aceptables de los mismos" como agentes farmacéuticos, están descritos por ejemplo en las patentes US nºs 4.509.612, 4.666.895, 4719.203, 4.777.163, 5.002.937, 4.971.958 y 4.958.839 y en las solicitudes de patente europea nºs 252.504 y 252.505, incorporadas a la presente como referencias para la descripción.

Métodos para la preparación de ácidos bisfosfónicos y sales farmacéuticamente aceptables de los mismos, pueden encontrarse p. ej., en las patentes U.S. nºs 3.962.432, 4.054.598, 4.267.108, 4.327.039, 4.407.761, 4.621.077,

4.624.947, 4.746.654, 4.922.077, 4.970.335, 5.019.651, 4.761.406, 4.876.248; en J. Org. Chem. 32, 4111 (1967) y en la solicitud de patente europea 252.504, incorporadas a la presente como referencia. Las sales farmacéuticamente aceptables de los ácidos bisfosfónicos pueden también emplearse en la presente invención. Ejemplos de sales básicas de ácidos bisfosfónicos incluyen las sales de amonio, sales de metal alcalino como potasio y sodio (incluyendo las sales mono, di y trisódicas) (las cuales son las preferidas), sales de metal alcalinotérreo tales como calcio y magnesio, sales con bases orgánicas tales como las sales de diciclohexilamina, N-metil-D-glucamina y sales con aminoácidos tales como la arginina, lisina, etcétera. Se prefieren las sales no tóxicas, fisiológicamente aceptables. Las sales pueden prepararse por métodos ya conocidos en la técnica, como se describen en la solicitud de la patente europea 252.504 ó en la patente US n° 4.922.077, incorporadas a la presente como referencia.

De preferencia, el medicamento contiene de 100 a 150 mg de un ácido ibandrónico o de una sal farmacéuticamente aceptable del mismo. De preferencia, el medicamento se administra como dosis simple.

En una versión preferida de la presente invención, el término "bisfosfonato" de la presente invención corresponde a compuestos de fórmula general



(I)

en donde A y X son independientemente entre sí, seleccionadas del grupo formado por hidrógeno, hidroxilo, halógeno, amino, SH, fenilo, alquilo, mono o dialquilamino, mono o dialquilaminoalquilo, alcoxilo, tioalquilo, tiofenilo, y conjuntos arilo o heteroarilo seleccionados del grupo formado por fenilo, piridilo, furanilo, pirrolidinilo, imidazolilo y bencilo, en donde el conjunto arilo o heteroarilo está opcionalmente substituido con alquilo.

En la fórmula química anterior, A puede incluir X, y X incluye A de forma que los dos conjuntos pueden formar parte de la misma estructura cíclica.

La fórmula química anterior pretende abarcar estructuras carbocíclicas, aromáticas y heteroaromáticas para los substituyentes A y/o X, p. ej., naftilo, quinolilo, isoquinolilo, adamantilo y clorofeniltio.

Estructuras preferidas son aquellas en las cuales A se selecciona del grupo formado por hidrógeno, hidroxilo y halógeno, y X se selecciona del grupo formado por alquilo, halógeno, tiofenilo, tioalquilo y dialquilaminoalquilo.

Las estructuras más preferidas son aquellas en las cuales A se selecciona del grupo formado por hidrógeno, hidroxilo y Cl, y X se selecciona del grupo formado por alquilo, Cl, clorofeniltio y dialquilaminoalquilo.

El ácido bisfosfónico preferido o su sal farmacéuticamente aceptable, se selecciona del grupo formado por alendronato, cimadronato, clodronato, EB-1053, tiludronato, etidronato, ibandronato, incadronato, minodronato, neridronato, olpadronato, risedronato, piridronato, pamidro-

nato, zolendronato o sales aceptables de los mismos, p. ej., la sal monosódica del ácido ibandrónico monohidrato.

El ácido ibandrónico (ácido 1-hidroxi-3-(N-metil-N-pentil)aminopropiliden-1,1-bisfosfónico) o las sales compatibles del mismo son particularmente preferidas, p. ej., la sal monosódica del ácido ibandrónico monohidrato.

Los bisfosfonatos y las sales farmacéuticamente aceptables, pueden administrarse solas o en combinación con otros fármacos activos para huesos, bien en combinaciones fijas o bien separadas tanto físicamente como en el tiempo, incluyendo hormonas tales como una hormona esteroide, p. ej., un estrógeno, un agonista parcial de estrógeno, o una combinación estrógeno-gestágeno; una calcitonina o análogo o derivado de la misma, p. ej., la hormona del salmón, de la anguila o la hormona del paratiroides calcitonina humana o análogos de las mismas, p. ej., PTH (1-84), PTH (1-34), PTH (1-36). PTH (1-38), PTH (1-31)NH2 o PPTS 893; un SERM (Selective Estrogen Receptor Modulator) ("Modulador receptor de estrógeno selectivo"), p. ej., raloxifene, lasofoxifene, TSE-434, FC1271, tibolone, vitamina D ó un análogo. Estos fármacos activos para el hueso adicionales, pueden administrarse más frecuentemente que el bisfosfonato.

Composiciones farmacéuticas apropiadas son ya conocidas en la especialidad y han sido descritas p. ej., en las patentes US nºs 6.143.326 y 6.294.196, las cuales se incorporan a la presente como referencia.

Para la preparación de comprimidos, comprimidos lacados, grageas o cápsulas de gelatina dura, los compuestos de la

presente invención pueden mezclarse con excipientes inorgánicos u orgánicos farmacéuticamente inertes. Ejemplos de excipientes adecuados para comprimidos, grageas o cápsulas de gelatina dura incluyen la lactosa, almidón de maíz o derivados de los mismo, talco o ácido esteárico o sales del mismo.

Las composiciones farmacéuticas pueden contener también agentes conservantes, agentes solubilizantes, agentes estabilizantes, agentes humectantes, emulsionantes, edulcorantes, colorantes, odorantes, sales para variar la presión osmótica, tampones, agentes para recubrimiento o antioxidantes. Pueden contener también otros agentes terapéuticamente valiosos. De preferencia, la composición farmacéutica es un comprimido recubierto con una película en el cual el núcleo del comprimido contiene 50 a 200 mg de un ácido bisfosfónico o una sal del mismo farmacéuticamente aceptable como se ha definido más arriba y uno o más excipientes farmacéuticamente aceptables seleccionados del grupo formado por lactosa, polivinilpirrolidona, celulosa microcristalina, crospovidona, ácido esteárico, dióxido de silicio y el recubrimiento del comprimido contiene uno o más excipientes farmacéuticamente aceptable seleccionados del grupo formado por hidroxipropilmetilcelulosa, dióxido de titanio, talco y polietilenglicol 6000. Estas composiciones son ya conocidas en la especialidad y están descritas por ejemplo en las patentes US n^{os} 6.143.326 y 6.294.196.

Otro aspecto de la presente invención es un método para el tratamiento, reducción o prevención de trastornos carac-

terizados por un aumento patológico de la resorción ósea, el cual comprende la administración a un mamífero de una cantidad efectiva de ácidos bisfosfónicos o sales aceptables de los mismos. Particularmente, la invención se refiere a un método para el tratamiento, reducción o prevención de transtornos caracterizados por un aumento patológico de la resorción ósea, el cual comprende la administración oral de una cantidad efectiva de un ácido bisfosfónico o una sal farmacéuticamente aceptable del mismo, en donde se administra aproximadamente de 50 a 250 mg de ácido bisfosfónico o una sal farmacéuticamente aceptable del mismo, y se administra en uno, dos o tres días consecutivos por mes. Como se ha indicado más arriba, la cantidad efectiva de ácido bisfosfónico o sal farmacéuticamente aceptable del mismo puede administrarse en forma de dosis simple o como subdosis múltiples.

De preferencia, el método comprende la administración de aproximadamente 50 a 250 mg, de preferencia aproximadamente 100 a 150 mg, de un bisfosfonato o una sal farmacéuticamente aceptable del mismo, dos o tres días consecutivos por mes. Aunque el método incluye la administración de la dosis mediante subdosis múltiples, el método aboga de preferencia por una dosis simple: Ejemplos para la administración de la dosis mediante subdosis múltiples son como sigue: si la dosis eficaz es de 150 mg. la dosis puede ser dos (2) subdosis de 75 mg administradas en un día o dos días consecutivos, o tres (3) subdosis de 50 mg administradas en un día o en dos o tres días consecutivos; si la dosis eficaz es de 100 mg, la dosis

puede ser dos (2) subdosis de 50 mg administradas en un día o dos días consecutivos, de preferencia en dos días consecutivos. El bisfosfonato preferido es el ibandronato o una sal farmacéuticamente aceptable del mismo, p. ej., la sal monosódica del ácido ibandrónico monohidrato.

De preferencia, en el método de acuerdo con la presente invención, el ácido bisfosfónico se selecciona del grupo formado por alendronato, cimadronato, clodronato, EB-1053, tiludronato, etidronato, ibandronato, incadronato, minodronato, neridronato, olpadronato, risedronato, piridronato, pamidronato, zolendronato o sales farmacéuticamente aceptables de los mismos. Con más preferencia el ácido bisfosfónico es el ibandronato o una sal farmacéuticamente aceptable del mismo, p. ej., la sal monosódica del ácido ibandrónico, monohidrato.

La invención se describe a continuación con referencia a las versiones ejemplificadas.

EJEMPLOS

EJEMPLO 1: Composición farmacéutica

El ejemplo muestra la composición de un comprimido de 50 mg. La composición y preparación de estos comprimidos ya son conocidas en la especialidad y están descritas por ejemplo en las patentes US nºs 6.143.326 y 6.294.196.

Pueden prepararse otras composiciones ajustando los ingredientes de acuerdo con la cantidad de bisfosfonato, p. ej., la sal monosódica del ácido ibandrónico monohidrato.

Comprimido de 50 mg recubierto con una película	
Componentes	**mg por comprimido**
Núcleo del comprimido:	
Sal monosódica del ácido ibandrónico, monohidrato	56.250
Lactosa monohidrato	92.750
Povidona K 25	5.000
Celulosa microcristalina	30.000
Crospovidona	10.000
Acido esteárico purificado	4.000
Dióxido de silicio coloidal	2.000
Recubrimiento del comprimido:	
Hidroxipropilmetilcelulosa	5.1425
Dióxido de titanio	2.4650
Talco	0.8925
Polietilenglicol 6.000	1.5000
Peso final:	**210.000**

REIVINDICACIONES

1. Un medicamento para administración oral caracterizado porque es un comprimido recubierto por una película, en donde el núcleo del comprimido comprende:

- 100 mg o 150 mg de un ácido bisfosfónico o una sal farmcéuticamente aceptable del mismo; y,
- uno o mas excipientes farmacéuticamente aceptables seleccionados del grupo conformado por: lactosa, polivinilpirrolidona, celulosa microcristalina, crospovidona, ácido esteárico y dióxido de silicio;

y en donde el recubrimiento del comprimido comprende uno o mas excipientes farmacéuticamente aceptables seleccionados entre el grupo conformado por: hidroxipropil metilcelulosa, dióxido de titanio, talco y polietilenglicol 6000.

2. El medicamento de la reivindicación 1, en donde el ácido bisfosfónico es el ácido ibandrónico o una sal farmacéuticamente aceptable del mismo.

3. El medicamento de las reivindicaciones 1 y 2, el cual comprende 100 mg de ácido bisfosfónico o una sal farmacéuticamente aceptable del mismo.

4. El medicamento de las reivindicaciones 1 y 2, el cual comprende 150 mg de ácido bisfosfónico o una sal farmacéuticamente aceptable del mismo.

5. El medicamento de acuerdo con cualquiera de las reivindicaciones 1 a 4, en donde el ácido bisfosfónico o la sal farmacéuticamente aceptable del mismo es la sal monosódica del ácido ibandrónico monohidrato.

F. Hoffmann La Roche AG 171

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Bonviva 150mg Film-Coated Tablets ■

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1. NAME OF THE MEDICINAL PRODUCT

Bonviva ▼150 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 150 mg ibandronic acid (as ibandronic sodium monohydrate).

Excipients

Each film-coated tablet contains 162.75 mg lactose monohydrate. For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

White to off white film-coated tablets, of oblong shape marked "BNVA" on one side, and "150" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of osteoporosis in postmenopausal women at increased risk of fracture (see section 5.1).

A reduction in the risk of vertebral fractures has been demonstrated, efficacy on femoral neck fractures has not been established.

4.2 Posology and method of administration

For oral use.

The recommended dose is one 150 mg film-coated tablet once a month. The tablet should preferably be taken on the same date each month.

Bonviva should be taken after an overnight fast (at least 6 hours) and 1 hour before the first food or drink (other than water) of the day (see section 4.5) or any other oral medicinal products or supplementation (including calcium):

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• Tablets should be swallowed whole with a glass of plain water (180 to 240 ml) while the patient is sitting or standing in an upright position. Patients should not lie down for 1 hour after taking Bonviva.

• Plain water is the only drink that should be taken with Bonviva. Please note that some mineral waters may have a higher concentration of calcium and therefore, should not be used.

• Patients should not chew or suck the tablet, because of a potential for oropharyngeal ulceration.

In case a dose is missed, patients should be instructed to take one Bonviva 150 mg tablet the morning after the tablet is remembered, unless the time to the next scheduled dose is within 7 days. Patients should then return to taking their dose once a month on their originally scheduled date.

If the next scheduled dose is within 7 days, patients should wait until their next dose and then continue taking one tablet once a month as originally scheduled.

Patients should not take two tablets within the same week.

Patients should receive supplemental calcium and / or vitamin D if dietary intake is inadequate (see section 4.4 and section 4.5).

Patients with renal impairment

No dosage adjustment is necessary for patients with mild or moderate renal impairment where creatinine clearance is equal or greater than 30 ml/min.

Bonviva is not recommended for patients with a creatinine clearance below 30 ml/min due to limited clinical experience (see section 4.4 and section 5.2).

Patients with hepatic impairment

No dosage adjustment is required (see section 5.2).

Elderly

No dosage adjustment is required (see section 5.2).

Children and adolescents

There is no experience in children.

4.3 Contraindications

- Hypocalcaemia (see section 4.4)

- Hypersensitivity to ibandronic acid or to any of the excipients.

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4.4 Special warnings and precautions for use

Hypocalcaemia must be corrected before starting Bonviva therapy. Other disturbances of bone and mineral metabolism should also be effectively treated. Adequate intake of calcium and vitamin D is important in all patients.

Bisphosphonates have been associated with dysphagia, oesophagitis and oesophageal or gastric ulcers. Therefore patients, especially those with a history of prolonged oesophageal transit time, should pay particular attention to and be able to comply with the dosing instructions (see section 4.2).

Physicians should be alert to signs or symptoms signalling a possible oesophageal reaction during therapy, and patients should be instructed to discontinue Bonviva and seek medical attention if they develop symptoms of oesophageal irritation such as new or worsening dysphagia, pain on swallowing, retrosternal pain, or heartburn.

Since NSAIDS and bisphosphonates are both associated with gastrointestinal irritation, caution should be taken during concomitant administration.

Due to limited clinical experience, Bonviva is not recommended for patients with a creatinine clearance below 30 ml/min (see section 4.2 and section 5.2).

Osteonecrosis of the jaw, generally associated with tooth extraction and/or local infection (including osteomyelitis) has been reported in patients with cancer receiving treatment regimens including primarily intravenously administered bisphosphonates. Many of these patients were also receiving chemotherapy and corticosteroids. Osteonecrosis of the jaw has also been reported in patients with osteoporosis receiving oral bisphosphonates.

A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g. cancer, chemotherapy, radiotherapy, corticosteroids, poor oral hygiene).

While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop osteonecrosis of the jaw while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis of the jaw. Clinical judgement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Drug-Food Interactions

Oral bioavailability of ibandronic acid is generally reduced in the presence of

food. In particular, products containing calcium and other multivalent cations (such as aluminium, magnesium, iron), including milk, are likely to interfere with absorption of Bonviva, which is consistent with findings in animal studies. Therefore, patients should fast overnight (at least 6 hours) before taking Bonviva and continue fasting for 1 hour following intake of Bonviva.

Drug-Drug Interactions

Calcium supplements, antacids and some oral medicinal products containing multivalent cations (such as aluminium, magnesium, iron) are likely to interfere with the absorption of Bonviva. Therefore, patients should not take other oral medicinal products for at least 6 hours before taking Bonviva and for 1 hour following intake of Bonviva. Pharmacokinetic interaction studies in postmenopausal women have demonstrated the absence of any interaction potential with tamoxifen or hormone replacement therapy (oestrogen). No interaction was observed when co-administered with melphalan/prednisolone in patients with multiple myeloma.

In healthy male volunteers and postmenopausal women, intravenous administration of ranitidine caused an increase in ibandronic acid bioavailability of about 20 %, probably as a result of reduced gastric acidity. However, since this increase is within the normal variability of the bioavailability of ibandronic acid, no dosage adjustment is considered necessary when Bonviva is administered with H2-antagonists or other active substances which increase gastric pH.

Metabolic interactions are not considered likely, since ibandronic acid does not inhibit the major human hepatic P450 isoenzymes and has been shown not to induce the hepatic cytochrome P450 system in rats. Furthermore, plasma protein binding is approximately 85 % - 87 % (determined *in vitro* at therapeutic drug concentrations), and thus there is a low potential for drug-drug interaction due to displacement. Ibandronic acid is eliminated by renal excretion only and does not undergo any biotransformation. The secretory pathway appears not to include known acidic or basic transport systems involved in the excretion of other active substances.

In a two-year study in postmenopausal women with osteoporosis (BM 16549), the incidence of upper gastrointestinal events in patients concomitantly taking aspirin or NSAIDs was similar in patients taking Bonviva 2.5 mg daily or 150 mg once monthly after one and two years.

Of over 1500 patients enrolled in study BM 16549 comparing monthly with daily dosing regimens of ibandronic acid, 14 % and 18 % of patients used histamine (H2) blockers or proton pump inhibitors after one and two years, respectively. Among these patients, the incidence of upper gastrointestinal events in the patients treated with Bonviva 150 mg once monthly was similar to that in patients treated with Bonviva 2.5 mg daily.

4.6 Pregnancy and lactation

There are no adequate data from the use of ibandronic acid in pregnant women. Studies in rats have shown some reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

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Bonviva should not be used during pregnancy.

It is not known whether ibandronic acid is excreted in human milk. Studies in lactating rats have demonstrated the presence of low levels of ibandronic acid in the milk following intravenous administration.

Bonviva should not be used during lactation.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

The safety of Bonviva 2.5 mg daily was evaluated in 1251 patients treated in 4 placebo-controlled clinical studies; 73 % of these patients came from the pivotal three-year treatment study (MF 4411). The overall safety profile of Bonviva 2.5 mg daily in all these studies was similar to that of placebo. The overall proportion of patients who experienced an adverse drug reaction, i.e. adverse event with a possible or probable relationship to trial medication, in the pivotal treatment study (MF 4411) was 19.8 % for Bonviva and 17.9 % for placebo.

In a two-year study in postmenopausal women with osteoporosis (BM 16549) the overall safety of Bonviva 150 mg once monthly and Bonviva 2.5 mg daily was similar. The overall proportion of patients who experienced an adverse drug reaction, i.e. adverse event with a possible or probable relationship to trial medication, was 22.7 % and 25.0 % for Bonviva 150 mg once monthly and 21.5 % and 22.5 % for Bonviva 2.5 mg daily after one and two years, respectively. The majority of adverse drug reactions were mild to moderate in intensity. Most cases did not lead to cessation of therapy.

Table 1 and table 2 list adverse drug reactions occurring in more than 1 % of patients treated with Bonviva 150 mg monthly or 2.5 mg daily in study BM 16549 and in patients treated with Bonviva 2.5 mg daily in study MF 4411. The tables show the adverse drug reactions in the two studies that occurred with a higher incidence than in patients treated with placebo in study MF 4411. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Data at one year from BM 16549 are represented in Table 1 and cumulative data for the two years from BM 16549 are represented in table 2.

Table 1: Common adverse drug reactions (>1/100, ≤ 1/10) in phase III osteoporosis studies that were considered by the investigator to be possibly or probably related to treatment - One year data from study BM 16549 and three year data from placebo-controlled fracture study MF 4411

	One year data in study BM 16549	Three year data in study MF 4411

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System Organ Class/ Adverse drug reaction	Bonviva 150 mg once monthly (N=396) (%)	Bonviva 2.5 mg daily (N=395) (%)	Bonviva 2.5 mg daily (N=977) (%)	Placebo (N=975) (%)
Gastrointestinal system				
Gastro-oesophageal reflux disease	0.5	1.0	0.4	0.1
Diarrhoea	2.5	1.8	1.4	1.0
Abdominal pain	3.5	2.8	2.1	2.9
Dyspepsia	3.3	5.8	4.3	2.9
Nausea	3.3	3.5	1.8	2.3
Flatulence	0.5	1.0	0.4	0.7
Nervous system				
Headache	0.8	1.5	0.8	0.6
General disorders				
Influenza like illness*	3.3	0.3	0.3	0.2
Fatigue	1.0	0.3	0.3	0.4
Musculoskeletal system				
Arthralgia	1.0	0.3	0.4	0.4
Myalgia	1.5	0.3	1.8	0.8
Skin disorders				
Rash	0.8	1.0	1.2	0.7

MedDRA version 6.1

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* Transient, influenza-like symptoms have been reported with Bonviva 150 mg once monthly, typically in association with the first dose. Such symptoms were generally of short duration, mild or moderate in intensity, and resolved during continuing treatment without requiring remedial measures. Influenza-like illness includes events reported as acute phase reaction or symptoms including myalgia, arthralgia, fever, chills, fatigue, nausea, loss of appetite, or bone pain.

Table 2: Cumulative common adverse drug reactions (>1/100, ≤ 1/10) in Phase III osteoporosis studies that were considered by the investigator to be possibly or probably related to treatment - Two year data from study BM 16549 and three year data from placebo-controlled fracture study MF 4411

	Two year cumulative data in study BM 16549		Three year data in study MF 4411	
System Organ Class/ Adverse drug reaction	Bonviva 150 mg once monthly (N=396) (%)	Bonviva 2.5 mg daily (N=395) (%)	Bonviva 2.5 mg daily (N=977) (%)	Placebo (N=975) (%)
Gastrointestinal system				
Gastritis	1.0	0.3	0.7	0.5
Gastro-oesophageal reflux disease	0.8	1.0	0.5	0.1
Oesophagitis	0	1.0	0.5	0.4
Diarrhoea	2.5	2.0	1.4	1.0
Abdominal pain	4.0	3.0	2.1	2.9
Dyspepsia	4.0	6.3	4.0	2.7
Nausea	3.0	3.5	1.8	2.3
Nervous system				
Headache	0.8	1.5	0.8	0.6
General disorders				
Influenza like illness*	3.3	0.3	0.3	0.2

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Musculoskeletal system				
Muscle cramp	0.5	1.0	0.1	0.4
Musculoskeletal pain	1.0	0.5	0	0
Arthralgia	1.0	0.5	0.4	0.4
Myalgia	1.5	0.3	1.8	0.8
Musculoskeletal stiffness	1.0	0	0	0
Skin disorders				
Rash	0.8	1.0	1.2	0.7

MedDRA version 7.1

* Transient, influenza-like symptoms have been reported with Bonviva 150 mg once monthly, typically in association with the first dose. Such symptoms were generally of short duration, mild or moderate in intensity, and resolved during continuing treatment without requiring remedial measures. Influenza-like illness includes events reported as acute phase reaction or symptoms including myalgia, arthralgia, fever, chills, fatigue, nausea, loss of appetite, or bone pain.

Adverse drug reactions occurring at a frequency of less than or equal to 1 %

The following list provides information on adverse drug reactions reported in study MF 4411 occurring more frequently with Bonviva 2.5 mg daily than with placebo and study BM 16549 occurring more frequently with Bonviva 150 mg once monthly than with Bonviva 2.5 mg daily. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness:

Uncommon (1/100 – 1/1,000)

Gastro-intestinal Disorders: gastritis, oesophagitis including oesophageal ulcerations or strictures, vomiting, dysphagia

Nervous System Disorders: dizziness

Musculoskeletal and Connective Tissue Disorders: back pain

Rare (1/1,000 – 1/10,000)

Gastro-intestinal Disorders: duodenitis

Immune System Disorders: hypersensitivity reactions

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Skin and Subcutaneous Tissue Disorders: angioedema, face oedema, urticaria

Patients with a previous history of gastrointestinal disease including patients with peptic ulcer without recent bleeding or hospitalisation, and patients with dyspepsia or reflux controlled by medication were included in the once monthly treatment study. For these patients, there was no difference in the incidence of upper gastrointestinal adverse events with the 150 mg once monthly regimen compared to the 2.5 mg daily regimen.

Laboratory test findings

In the pivotal three-year study with Bonviva 2.5 mg daily (MF 4411) there was no difference compared with placebo for laboratory abnormalities indicative of hepatic or renal dysfunction, an impaired haematologic system, hypocalcaemia or hypophosphataemia. Similarly, no differences were noted between the groups in study BM 16549 after one and two years.

Post-marketing Experience

Osteonecrosis of the jaw has been reported in patients treated by bisphosphonates. The majority of the reports refer to cancer patients, but such cases have also been reported in patients treated for osteoporosis. Osteonecrosis of the jaw is generally associated with tooth extraction and / or local infection (including osteomyelitis). Diagnosis of cancer, chemotherapy, radiotherapy, corticosteroids and poor oral hygiene are also deemed as risk factors (see section 4.4).

4.9 Overdose

No specific information is available on the treatment of over dosage with Bonviva.

However, based on a knowledge of this class of compounds, oral over-dosage may result in upper gastrointestinal adverse reactions (such as upset stomach, dyspepsia, oesophagitis, gastritis, or ulcer) or hypocalcaemia. Milk or antacids should be given to bind Bonviva, and any adverse reactions treated symptomatically. Owing to the risk of oesophageal irritation, vomiting should not be induced and the patient should remain fully upright.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Bisphosphonates, ATC code: M05B A06

Mechanism of action

Ibandronic acid is a highly potent bisphosphonate belonging to the nitrogen-containing group of bisphosphonates, which act selectively on bone tissue and specifically inhibit osteoclast activity without directly affecting bone formation. It does not interfere with osteoclast recruitment. Ibandronic acid leads to

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progressive net gains in bone mass and a decreased incidence of fractures through the reduction of elevated bone turnover towards premenopausal levels in postmenopausal women.

Pharmacodynamic effects

The pharmacodynamic action of ibandronic acid is inhibition of bone resorption. *In vivo*, ibandronic acid prevents experimentally induced bone destruction caused by cessation of gonadal function, retinoids, tumours or tumour extracts. In young (fast growing) rats, the endogenous bone resorption is also inhibited, leading to increased normal bone mass compared with untreated animals.

Animal models confirm that ibandronic acid is a highly potent inhibitor of osteoclastic activity. In growing rats, there was no evidence of impaired mineralization even at doses greater than 5,000 times the dose required for osteoporosis treatment.

Both daily and intermittent (with prolonged dose-free intervals) long-term administration in rats, dogs and monkeys was associated with formation of new bone of normal quality and maintained or increased mechanical strength even at doses in the toxic range. In humans, the efficacy of both daily and intermittent administration with a dose-free interval of 9-10 weeks of ibandronic acid was confirmed in a clinical trial (MF 4411), in which Bonviva demonstrated anti-fracture efficacy.

In animal models ibandronic acid produced biochemical changes indicative of dose-dependent inhibition of bone resorption, including suppression of urinary biochemical markers of bone collagen degradation (such as deoxypyridinoline, and cross-linked N-telopeptides of type I collagen (NTX)).

In a Phase 1 bioequivalence study conducted in 72 postmenopausal women receiving 150 mg orally every 28 days for a total of four doses, inhibition in serum CTX following the first dose was seen as early as 24 hours post-dose (median inhibition 28 %), with median maximal inhibition (69 %) seen 6 days later. Following the third and fourth dose, the median maximum inhibition 6 days post dose was 74 % with reduction to a median inhibition of 56 % seen 28 days following the fourth dose. With no further dosing, there is a loss of suppression of biochemical markers of bone resorption.

Clinical efficacy

Independent risk factors, for example, low BMD, age, the existence of previous fractures, a family history of fractures, high bone turnover and low body mass index should be considered in order to identify women at increased risk of osteoporotic fractures.

Bonviva 150 mg once monthly

Bone mineral density (BMD)

Bonviva 150 mg once monthly was shown to be at least as effective as Bonviva 2.5 mg daily at increasing BMD in a two year, double-blind, multicentre study

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(BM 16549) of postmenopausal women with osteoporosis (lumbar spine BMD T score below -2.5 SD at baseline). This was demonstrated in both the primary analysis at one year and in the confirmatory analysis at two years endpoint (Table 3).

Table 3: Mean relative change from baseline of lumbar spine, total hip, femoral neck and trochanter BMD after one year (primary analysis) and two years of treatment (Per-Protocol Population) in study BM 16549.

	One year data in study BM 16549		Two year data in study BM 16549	
Mean relative changes from baseline % [95% CI]	Bonviva 2.5 mg daily (N=318)	Bonviva 150 mg once monthly (N=320)	Bonviva 2.5 mg daily (N=294)	Bonviva 150 mg once monthly (N=291)
Lumbar spine L2-L4 BMD	3.9 [3.4, 4.3]	4.9 [4.4, 5.3]	5.0 [4.4, 5.5]	6.6 [6.0, 7.1]
Total hip BMD	2.0 [1.7, 2.3]	3.1 [2.8, 3.4]	2.5 [2.1, 2.9]	4.2 [3.8, 4.5]
Femoral neck BMD	1.7 [1.3, 2.1]	2.2 [1.9, 2.6]	1.9 [1.4, 2.4]	3.1 [2.7, 3.6]
Trochanter BMD	3.2 [2.8, 3.7]	4.6 [4.2, 5.1]	4.0 [3.5, 4.5]	6.2 [5.7, 6.7]

Furthermore, Bonviva 150 mg once monthly was proven superior to Bonviva 2.5 mg daily for increases in lumbar spine BMD in a prospectively planned analysis at one year, $p=0.002$, and at two years, $p<0.001$.

At one year (primary analysis), 91.3 % ($p=0.005$) of patients receiving Bonviva 150 mg once monthly had a lumbar spine BMD increase above or equal to baseline (BMD responders), compared with 84.0 % of patients receiving Bonviva 2.5 mg daily. At two years, 93.5 % ($p=0.004$) and 86.4 % of patients receiving Bonviva 150 mg once monthly or Bonviva 2.5 mg daily, respectively, were responders.

For total hip BMD, 90.0 % ($p<0.001$) of patients receiving Bonviva 150 mg once monthly and 76.7 % of patients receiving Bonviva 2.5 mg daily had total hip BMD increases above or equal to baseline at one year. At two years 93.4 % ($p<0.001$) of patients receiving Bonviva 150 mg once monthly and 78.4 %, of patients receiving Bonviva 2.5 mg daily had total hip BMD increases above or equal to baseline.

When a more stringent criterion is considered, which combines both lumbar spine and total hip BMD, 83.9 % ($p<0.001$) and 65.7 % of patients receiving Bonviva 150 mg once monthly or Bonviva 2.5 mg daily, respectively, were responders at one year. At two years, 87.1 % ($p<0.001$) and 70.5 %,of patients met this

criterion in the 150 mg monthly and 2.5 mg daily arms respectively.

Biochemical markers of bone turn-over

Clinically meaningful reductions in serum CTX levels were observed at all time points measured, i.e. months 3, 6, 12 and 24. After one year (primary analysis) the median relative change from baseline was -76 % for Bonviva 150 mg once monthly and -67 % for Bonviva 2.5 mg daily. At two years the median relative change was -68 % and -62 %, in the 150 mg monthly and 2.5 mg daily arms respectively.

At one year, 83.5 % (p= 0.006) of patients receiving Bonviva 150 mg once monthly and 73.9 % of patients receiving Bonviva 2.5 mg daily were identified as responders (defined as a decrease ≥ 50 % from baseline). At two years 78.7 % (p=0.002) and 65.6 % of patients were identified as responders in the 150 mg monthly and 2.5 mg daily arms respectively.

Based on the results of study BM 16549, Bonviva 150 mg once monthly is expected to be at least as effective in preventing fractures as Bonviva 2.5 mg daily.

Bonviva 2.5 mg daily

In the initial three-year, randomised, double-blind, placebo-controlled, fracture study (MF 4411), a statistically significant and medically relevant decrease in the incidence of new radiographic morphometric and clinical vertebral fractures was demonstrated (table 4). In this study, Bonviva was evaluated at oral doses of 2.5 mg daily and 20 mg intermittently as an exploratory regimen. Bonviva was taken 60 minutes before the first food or drink of the day (post-dose fasting period). The study enrolled women aged 55 to 80 years, who were at least 5 years postmenopausal, who had a BMD at lumbar spine of 2 to 5 SD below the premenopausal mean (T-score) in at least one vertebra [L1-L4], and who had one to four prevalent vertebral fractures. All patients received 500 mg calcium and 400 IU vitamin D daily. Efficacy was evaluated in 2,928 patients. Bonviva 2.5 mg administered daily, showed a statistically significant and medically relevant reduction in the incidence of new vertebral fractures. This regimen reduced the occurrence of new radiographic vertebral fractures by 62 % (p=0.0001) over the three year duration of the study. A relative risk reduction of 61 % was observed after 2 years (p=0.0006). No statistically significant difference was attained after 1 year of treatment (p=0.056). The anti-fracture effect was consistent over the duration of the study. There was no indication of a waning of the effect over time.

The incidence of clinical vertebral fractures was also significantly reduced by 49 % (p=0.011). The strong effect on vertebral fractures was furthermore reflected by a statistically significant reduction of height loss compared to placebo (p<0.0001).

Table 4: Results from 3 years fracture study MF 4411 (%, 95 % CI)		
	Placebo	Bonviva 2.5 mg daily

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	(N=974)	(N=977)
Relative Risk Reduction New morphometric vertebral fractures		62 % (40.9, 75.1)
Incidence of new morphometric vertebral fractures	9.56 % (7.5, 11.7)	4.68 % (3.2,6.2)
Relative risk reduction of clinical vertebral fracture		49 % (14.03, 69.49)
Incidence of clinical vertebral fracture	5.33 % (3.73, 6.92)	2.75 % (1.61, 3.89)
BMD – mean change relative to baseline lumbar spine at year 3	1.26 % (0.8, 1.7)	6.54 % (6.1, 7.0)
BMD – mean change relative to baseline total hip at year 3	-0.69 % (-1.0, -0.4)	3.36 % (3.0, 3.7)

The treatment effect of Bonviva was further assessed in an analysis of the subpopulation of patients who at baseline had a lumbar spine BMD T-score below −2.5. The vertebral fracture risk reduction was very consistent with that seen in the overall population.

Table 5: Results from 3 years fracture study MF 4411 (%, 95 % CI) for patients with lumbar spine BMD T-score below −2.5 at baseline		
	Placebo (N=587)	Bonviva 2.5 mg daily (N=575)
Relative Risk Reduction New morphometric vertebral fractures		59 % (34.5, 74.3)
Incidence of new morphometric vertebral fractures	12.54 % (9.53, 15.55)	5.36 % (3.31, 7.41)
Relative risk reduction of clinical vertebral fracture		50 % (9.49, 71.91)
Incidence of clinical vertebral fracture	6.97 % (4.67, 9.27)	3.57 % (1.89, 5.24)

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BMD – mean change relative to baseline lumbar spine at year 3	1.13 % (0.6, 1.7)	7.01 % (6.5, 7.6)
BMD – mean change relative to baseline total hip at year 3	-0.70 % (-1.1, -0.2)	3.59 % (3.1, 4.1)

In the overall patient population of the study MF4411, no reduction was observed for non-vertebral fractures, however daily ibandronate appeared to be effective in a high-risk subpopulation (femoral neck BMD T-score < -3.0), where a non-vertebral fracture risk reduction of 69% was observed.

Daily treatment with 2.5 mg resulted in progressive increases in BMD at vertebral and nonvertebral sites of the skeleton.

Three-year lumbar spine BMD increase compared to placebo was 5.3 % and 6.5 % compared to baseline. Increases at the hip compared to baseline were 2.8 % at the femoral neck, 3.4 % at the total hip, and 5.5 % at the trochanter.

Biochemical markers of bone turnover (such as urinary CTX and serum Osteocalcin) showed the expected pattern of suppression to premenopausal levels and reached maximum suppression within a period of 3-6 months.

A clinically meaningful reduction of 50 % of biochemical markers of bone resorption was observed as early as one month after start of treatment with Bonviva 2.5 mg.

Following treatment discontinuation, there is a reversion to the pathological pre-treatment rates of elevated bone resorption associated with postmenopausal osteoporosis.

The histological analysis of bone biopsies after two and three years of treatment of postmenopausal women showed bone of normal quality and no indication of a mineralization defect.

5.2 Pharmacokinetic properties

The primary pharmacological effects of ibandronic acid on bone are not directly related to actual plasma concentrations, as demonstrated by various studies in animals and humans.

Absorption

The absorption of ibandronic acid in the upper gastrointestinal tract is rapid after oral administration and plasma concentrations increase in a dose-proportional manner up to 50 mg oral intake, with greater than dose-proportional increases seen above this dose. Maximum observed plasma concentrations were reached within 0.5 to 2 hours (median 1 hour) in the fasted state and absolute bioavailability was about 0.6 %. The extent of absorption is impaired when taken together with food or beverages (other than plain water). Bioavailability is reduced by about 90 % when Bonviva is administered with a standard breakfast

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in comparison with bioavailability seen in fasted subjects. There is no meaningful reduction in bioavailability provided ibandronic acid is taken 60 minutes before the first food of the day. Both bioavailability and BMD gains are reduced when food or beverage is taken less than 60 minutes after Bonviva is ingested.

Distribution

After initial systemic exposure, ibandronic acid rapidly binds to bone or is excreted into urine. In humans, the apparent terminal volume of distribution is at least 90 l and the amount of dose reaching the bone is estimated to be 40-50 % of the circulating dose. Protein binding in human plasma is approximately 85 % - 87 % (determined *in vitro* at therapeutic drug concentrations), and thus there is a low potential for drug-drug interaction due to displacement.

Metabolism

There is no evidence that ibandronic acid is metabolised in animals or humans.

Elimination

The absorbed fraction of ibandronic acid is removed from the circulation via bone absorption (estimated to be 40 - 50 % in postmenopausal women) and the remainder is eliminated unchanged by the kidney. The unabsorbed fraction of ibandronic acid is eliminated unchanged in the faeces.

The range of observed apparent half-lives is broad, the apparent terminal half-life is generally in the range of 10-72 hours. As the values calculated are largely a function of the duration of study, the dose used, and assay sensitivity, the true terminal half-life is likely to be substantially longer, in common with other bisphosphonates. Early plasma levels fall quickly reaching 10 % of peak values within 3 and 8 hours after intravenous or oral administration respectively.

Total clearance of ibandronic acid is low with average values in the range 84-160 ml/min. Renal clearance (about 60 mL/min in healthy postmenopausal females) accounts for 50-60 % of total clearance and is related to creatinine clearance. The difference between the apparent total and renal clearances is considered to reflect the uptake by bone.

Pharmacokinetics in special clinical situations

Gender

Bioavailability and pharmacokinetics of ibandronic acid are similar in men and women.

Race

There is no evidence for any clinically relevant inter-ethnic differences between Asians and Caucasians in ibandronic acid disposition. There are few data available on patients of African origin.

Patients with renal impairment

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Renal clearance of ibandronic acid in patients with various degrees of renal impairment is linearly related to creatinine clearance.

No dosage adjustment is necessary for patients with mild or moderate renal impairment (CLcr equal or greater than 30 ml/min), as shown in study BM 16549 where the majority of patients had mild to moderate renal impairment.

Subjects with severe renal failure (CLcr less than 30 ml/min) receiving daily oral administration of 10 mg ibandronic acid for 21 days, had 2-3 fold higher plasma concentrations than subjects with normal renal function and total clearance of ibandronic acid was 44 ml/min. After intravenous administration of 0.5 mg, total, renal, and non-renal clearances decreased by 67 %, 77 % and 50 %, respectively, in subjects with severe renal failure but there was no reduction in tolerability associated with the increase in exposure. Due to the limited clinical experience, Bonviva is not recommended in patients with severe renal impairment (see section 4.2 and section 4.4) . The pharmacokinetics of ibandronic acid was not assessed in patients with end-stage renal disease managed by other than haemodialysis. The pharmacokinetics of ibandronic acid in these patients is unknown, and ibandronic acid should not be used under these circumstances.

Patients with hepatic impairment

There are no pharmacokinetic data for ibandronic acid in patients who have hepatic impairment. The liver has no significant role in the clearance of ibandronic acid which is not metabolised but is cleared by renal excretion and by uptake into bone. Therefore dosage adjustment is not necessary in patients with hepatic impairment.

Elderly

In a multivariate analysis, age was not found to be an independent factor of any of the pharmacokinetic parameters studied. As renal function decreases with age this is the only factor to take into consideration (see renal impairment section).

Children and adolescents

There are no data on the use of Bonviva in these age groups.

5.3 Preclinical safety data

Toxic effects, e.g signs of renal damage, were observed in dogs only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Mutagenicity/Carcinogenicity:

No indication of carcinogenic potential was observed. Tests for genotoxicity revealed no evidence of genetic activity for ibandronic acid.

Reproductive toxicity:

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There was no evidence for a direct foetal toxic or teratogenic effect of ibandronic acid in orally treated rats and rabbits and there were no adverse effects on the development in F_1 offspring in rats at an extrapolated exposure of at least 35 times above human exposure. Adverse effects of ibandronic acid in reproductive toxicity studies in the rat were those observed with bisphosphonates as a class. They include a decreased number of implantation sites, interference with natural delivery (dystocia), and an increase in visceral variations (renal pelvis ureter syndrome).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose monohydrate

Povidone

Cellulose, microcrystalline

Crospovidone

Stearic acid

Silica, colloidal anhydrous

Tablet coat

Hypromellose

Titanium dioxide E171

Talc

Macrogol 6,000

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

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Bonviva 150 mg film-coated tablets are supplied in blisters (PVC/PVDC) containing 1 or 3 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Roche Registration Limited

6 Falcon Way

Shire Park

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AL7 1TW

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8. MARKETING AUTHORISATION NUMBER(S)

EU/1/03/265/003

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23.02.2004

10. DATE OF REVISION OF THE TEXT

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Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMEA) http://www.emea.eu.int/

http://emc.medicines.org.uk/emc/assets/c/html/DisplayDoc.asp?DocumentID=16730

SUPPORTING INFORMATION

Patient Information Leaflet:
Bonviva 150mg Film Coated Tablets

Alternative format PIL:

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Bonviva 150mg Film Coated Tablets (new window)

Medicine Guide:
Bonviva (new window)

US006143326A

United States Patent [19]

Möckel et al.

[11] **Patent Number: 6,143,326**

[45] **Date of Patent: *Nov. 7, 2000**

[54] **ORAL PHARMACEUTICAL PREPARATION CONTAINING IBANDRONAT**

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[*] Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

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[52] **U.S. Cl.** **424/482**; 424/480

[58] **Field of Search** 424/480, 482

[56] **References Cited**

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Primary Examiner—Thurman K. Page
Assistant Examiner—A. Berman
Attorney, Agent, or Firm—Arent Fox Kintner Plotkin Kahn

[57] **ABSTRACT**

The invention is directed to well-tolerated pharmaceutical compositions for oral application, containing ibandronate or a physiologically tolerable salt thereof as active substance, the administration form consisting of an active substance-containing inner portion enclosed in such fashion by a coat free of active substance that rapid release of the active substance takes place.

3 Claims, No Drawings

forming agents mentioned above may be used according to the invention. Here, the polymers may be used alone as well as in mixtures of multiple polymers, and also together with other adjuvants, if necessary.

In the following, the invention will be illustrated by way of embodiments which are not intended as limitation.

For example, The ibandronate active substance is employed in amounts of 0.1–100 mg per single dosage unit. Preferably, the dosage is at least ca. 1 mg, 5 mg, 10 mg, or 20 mg as lower limit for the amount of active substance in a single administration form. The upper limit is about 250 mg, particularly 100 mg and 50 mg, respectively.

EXAMPLE 1

Ibandronate-containing core: Ibandronate dose [mg] in 200 mg tablet core:	10.0	20.0	50.0
Ibandronate-free coat [mg]:			
Methylhydroxypropylcellulose	5.1425	5.1425	5.1425
Titanium dioxide	2.4650	2.4650	2.4650
Macrogol	1.5000	1.5000	1.5000
Talc	0.8925	0.8925	0.8925
Total film coated	10.0000	10.0000	10.0000

Film-coating is carried out in common apparatus. Coating conditions: tablet charge 140 kg; feed air temperature: 60° C.

EXAMPLE 2

Ibandronate-containing core: Ibandronate dose in 100 mg tablet core [mg]:	0.1	2.5	5.0
Ibandronate-free coat [mg]:			
Methylhydroxypropylcellulose	2.057	2.057	2.057
Titanium dioxide	0.986	0.986	0.986
Macrogol	0.600	0.600	0.600
Talc	0.357	0.357	0.357
Total film coated	4.000	4.000	4.000

Film-coating in a conventional 250 l tablet coating tank. Coating conditions: tablet charge 144 kg.

EXAMPLE 3

Ibandronate-containing core: Ibandronate dose [mg] in 200 mg tablet core:	10.0	20.0	50.0
Ibandronate-free coat [mg]:			
Talc	2.00	2.00	2.00
Lactose	1.40	1.40	1.40
Methylhydroxypropylcellulose	0.80	0.80	0.80
Titanium dioxide	0.80	0.80	0.80
Macrogol	0.40	0.40	0.40
Ethyl methyl methacrylate copolymer*	0.04	0.04	0.04
Polysorbate	0.04	0.04	0.04
Total film coated	5.48	5.48	5.48

*Employed in the form of Eudragit ™ NE 30 D as an aqueous dispersion.

Film-coating in a conventional 15 l tablet coating tank. Coating conditions: tablet charge 13.0 kg.

EXAMPLE 4

Ibandronate-containing core: Ibandronate dose [mg] in 86 mg tablet core:	10
Ibandronate-free coat [mg]:	
Saccharose	37.844
White clay	8.138
Talc	1.000
Macrogol	2.848
Glucose syrup	2.035
Titanium dioxide	1.628
Polyvidone	0.407
Montan glycol wax	0.100
Total tablet coating applied	54.000

Tablet coating in a conventional 15 l tablet coating tank with dip pipe.

EXAMPLE 7

Ibandronate in laminated tablet	
Ibandronate-containing core:	
Final weight:	86 mg
Format of core:	7 mm in diameter, plane, with facettes
Ibandronate dose in tablet core:	10 mg
Ibandronate-free coat:	
Lactose	270 mg
Microcrystalline cellulose:	90 mg
Pressing tool:	12 mm in diameter
Final weight of laminated tablet:	446 mg

Pressing by means of a hand press using conventional procedures.

What is claimed is:

1. A method of treating a bone disease in a patient in need thereof, comprising orally administering to the patient a pharmaceutical formulation comprising a tablet core containing about 0.1 to 100 mg of ibandronate and a coating which is free of ibandronate and has the following proportional composition:

(a) about 51.425% by weight of methylhydroxypropylcellulose;

(b) about 24.650% by weight of titanium dioxide;

(c) about 15.000% by weight of polyethylene glycol; and

(d) about 8.925% by weight of talc.

2. The method of claim 1, wherein the bone disease is related to a disorder in calcium metabolism.

3. The method of claim 1, wherein the bone disease is selected from the group consisting of hypercalcemia, osteoporosis, tumor osteolysis, and Paget's disease.

* * * * *

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International Bureau

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A1

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(74) Agent: WITTE, Hubert; Grenzacherstrasse 124, CH–4070 Basle (CH).

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Published
With international search report.

(54) Title: PROCESS FOR THE PREPARATION OF ORAL PHARMACEUTICAL COMPOSITIONS COMPRISING BIPHOSPHONATES

(57) Abstract

The invention relates to a process for the preparation of bisphonate–containing pharmaceutical compositions for oral application, wherein the active substance is wet–granulated in manner known per se in a fluidised–bed granulator using adjuvants which have no abrasive action and wherein the wet granulate is then dried in the fluidised bed, screened through a screen having a suitable mesh width and further processed by techniques known per se to form pharmaceutical compositions.

Example 1 (Comparative example):

Production of ibandronate 2.5 mg capsules after granulation in a high-speed mixer/granulator (batch size for 45.000 capsules).

Constituents		g
Na-Ibandronate	120.24	
Lactose		7934.76
Polyvinyl pyrrolidone		202.50
Polyvinyl pyrrolidone, cross-linked (disintegrant)		562.50
Stearic acid (lubricant)		180.00

The amount of active substance per capsule is equivalent to 2.5 mg of free acid.

Lactose, ibandronate and polyvinyl pyrrolidone were mixed for 2 minutes at a fill factor of 50% in a high-speed mixer/granulator (Diosna type) and then granulated with water for 8 minutes. The wet granulate was dried in a fluidised bed (Aeromatic-type apparatus), passed through an 0.8 mm screen, mixed with disintegrant and lubricant (Rhoenrad-type mixer, mixing time 10 minutes) and encapsulated in size-2 hard gelatine capsules without compression in a capsule machine (type MG2/G36) having a capacity of 20,000 capsules per hour.

Set weight of filling:	200.0 mg
Actual weight of filling according to in-process control:	200.9 mg

Content of active substance found in capsules produced in this way: 94.8% ± 5.2% (n = 10 individual measurements).

Example 2 (Comparative example):

Production of ibandronate 1.0 mg capsules after granulation in a high-speed mixer/granulator (batch size for 5000 capsules).

Constituents		g
Na-Ibandronate	5.345	
Lactose		999.655
Polyvinyl pyrrolidone		22.500
Polyvinyl pyrrolidone, cross-linked (disintegrant)		62.500
Stearic acid (lubricant)		10.000

The amount of active substance per capsule is equivalent to 1.0 mg of free acid.

Lactose, ibandronate and polyvinyl pyrrolidone were mixed for 2 minutes in a high-speed mixer/granulator (Diosna type) and then granulated with water for 10 minutes. The wet granulate was dried in a fluidised bed (Aeromatic-type apparatus), screened through an 0.8 mm screen, mixed with disintegrant and lubricant (Rhoenrad-type mixer, mixing time 10 minutes) and enclosed in size-2 hard gelatine capsules in a capsule machine (type KFM Harro Höfliger).

Set weight of filling: 220.00 mg
Actual weight of filling according to

in-process control: 220.05 mg
Content of active substance found in the capsules produced in this way: 94.9% ± 1.9%
(n = 10 individual measurements)

Example 3:

Production of ibandronate 1.0 mg tablets after granulation in a fluidised bed (batch size for 60.000 tablets).

Constituents	g
Na-Ibandronate	64.14
Lactose	4405.86
Polyvinyl pyrrolidone	150.00
Polyvinyl pyrrolidone, cross-linked (disintegrant)	300.00
Stearic acid (lubricant)	120.00
Microcrystalline cellulose	900.00
Colloidal SiO_2 (flow agent)	60.0

The amount of active substance per tablet is equivalent to 1.0 mg of free acid.

Lactose and 600 g microcrystalline cellulose were granulated with an aqueous solution of polyvinyl pyrrolidone and ibandronate in a fluidised-bed granulator (Aeromatic type). The wet granulate was dried in the fluidised bed (Aeromatic type), passed through a 1.0 mm screen, mixed with disintegrant, lubricant, flow-regulator and 300 g microcrystalline cellulose (Turbula-type mixer, mixing time 5 minutes)

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
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Patente de Invención ☒ Patente de Modelo de Utilidad ☐

Vía Nacional ☐

Vía PCT (fase nacional) ☒ Cap.I ☐ Cap. II ☒

No. Sol. Internacional PCT/EP03/04629
Fecha de Presentación Internal. 02 de Mayo de 2003

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

Descripción:	Folios: 61 a 103 como se radicó inicialmente
Reivindicaciones:	Folios 18 a 20 como se radicó inicialmente
	Folios 51 a 52 modificadas en fase nacional
	Folios 109 a 110 modificadas en fase nacional
	Folios 170 modificadas en fase nacional
Prioridad:	Folios: 1
	10 de Mayo de 2002, EP, 02010136.6

Respuesta del solicitante: Folios: 93 a 123, 141 a 169, 171 a 190

2. Objeto de la invención

- Título de la solicitud: **"ÁCIDO BIFOSFÓNICO PARA EL TRATAMIENTO Y PREVENCIÓN DE OSTEOPOROSIS"** Folio 1.

El objeto de la presente solicitud de patente de invención consiste en el empleo de los ácidos bifosfónicos o las sales farmacéuticamente aceptables de los mismos, especialmente el ácido ibandrónico para la prevención y tratamiento de la osteoporosis.

El problema planteado en esta solicitud es la prevención o tratamiento de trastornos caracterizados por un aumento patológico de la resorción ósea.

Para solucionar este problema técnico la solicitud en estudio proporciona un medicamento de un ácido bifosfónicos o las sales farmacéuticamente aceptables de los mismos.

- **Clasificación Internacional de Patentes (IPC):** *A61K31/663; A61P19/10*

3. Determinación del Estado de la Técnica

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es: 13/11/2000 se encontraron los siguientes documentos del estado de la técnica relacionados, que pueden afectar la patentabilidad del objeto de la presente solicitud:

N°	Documento	Título	Fecha de publicación
D1	US 6,143,326	"Oral pharmaceutical preparation containing ibandronat"	30/10/1997
D2	WO 00/21541	"Process for the preparation of oral pharmaceutical compositions comprising biphosphonates"	20/04/2000

7. Análisis de patentabilidad (artículo 14 D486)

Nivel inventivo (artículo18 D486)

La reivindicación 1 se refiere a un medicamento para administración oral caracterizado porque es un comprimido recubierto por una película en donde el núcleo comprimido comprende:

- 100 mg o 150mg de un ácido bifosfónico o una sal farmacéuticamente aceptable del mismo y
- Uno o más excipientes farmacéuticamente aceptables seleccionados del grupo conformado por: lactosa, polivinilpirrolidona, celulosa microcristalina, crospovidona, ácido esteárico y dióxido de silicio y en donde el recubrimiento del comprimido comprende uno o más excipientes farmacéuticamente aceptables seleccionados entre el grupo conformado por: hidroxipropil metilcelulosa, dióxido de titanio, talco y polietilénglicol 6000

Recubierta

D1 divulga una formulación que comprende un núcleo de tableta que contiene entre **0.1 a 100mg de ibandronato** y una cubierta la cual es libre de ibandronato con la siguiente proporción: (Ver columna 6, líneas 46-56)

- **51.425%** por peso de **hidroxipropilmetilcelulosa**
- **24.650%** por peso de **dióxido de titanio**
- **15.000%** por peso de **polietilénglicol**
- **8.925%** por peso de **talco**

El ejemplo de la solicitud presentada utiliza en las tabletas de 50mg de ibandronato los mismos excipientes enunciados en **D1** para la película de recubrimiento donde se utilizan como excipientes: hidroxipropilmetilcelulosa, óxido de titanio, talco y Polietilénglicol por considerarse contenida, superpuesta y sugerida en la película de **D1** (Ver folio 169):

Tabla 1 "Película"

Solicitud presentada-Recubrimiento	**D1**
Hidroxipropilmetilcelulosa	SI (Ver columna 6, línea 51)
Dióxido de Titanio	SI (Ver columna 6, línea 52)
Talco	SI (Ver columna 6, línea 54)
Polietilénglicol 6000	SI (Ver columna 6, línea 53)

Núcleos:

D2 divulga previamente un proceso para la preparación de composiciones farmacéuticas orales que comprenden bifosfonatos. (Ver resumen)

El ibandronato es la sustancia activa preferida en **D2** particularmente en la forma de monohidrato de ibandronato sódico en una proporción hasta 50mg. (Ver página 6, líneas 1-7)

El ejemplo 3 y 4 de **D2**, enseñan formulaciones para tabletas las cuales contienen lactosa, polivinilpirrolidona, celulosa microcristalina, crospovidona, ácido esteárico y dióxido de silicio (Ver página 10 y 11).

La reivindicación 7 enseña que los adyuvantes usados se encuentran en las proporciones de lactosa en 1-99% por peso, polivinilpirrolidona en 0.1-20% por peso, celulosa microcristalina en 1-99% por peso. (Ver página 14, líneas 8-11-D2)

La reivindicación 9 enseña que el proceso aplica a tabletas recubiertas. (Ver página 14, líneas 19-20-**D2**)

La reivindicación 10 se refiere al peso de ácido esteárico a la mezcla en una proporción de 0.05-3% (Ver página 14, líneas 24-26-**D2**)

El solicitante en el ejemplo enseña los mismos componentes previamente divulgados para el núcleo de las tabletas tales como lactosa en 1-99% por peso, polivinilpirrolidona en 0.1-20% por peso, celulosa microcristalina en 1-99% por peso, crospovidona y dióxido de silicio (Ver folio 50).

Tabla 1 "Núcleos"

Solicitud presentada Núcleos	**D2** (Ejemplo 3-Página 10)
Lactosa	SI
Polivinilpirrolidona	SI
Celulosa Microcristalina	SI (Ver columna 6, línea 54)
Crospovidona	SI
Ácido esteárico	SI
Dióxido de Silicio	SI

Es evidente para el experto en la materia que de acuerdo a lo previamente divulgado en **D1** y **D2**, se obtendría el medicamento oral de ibandronato monosódico monohidrato en comprimidos recubiertos de 100mg o 150mg, empleando los mismos

excipientes antes enseñados previamente tales como lactosa, polivinilpirrolidona, celulosa microcristalina, crospovidona, ácido esteárico y dióxido de silicio e hidroxipropilmetilcelulosa en los núcleos, y óxido de titanio, talco y polietilénglicol en la recubierta, la solicitud por lo tanto carece de nivel inventivo.

El problema técnico planteado en esta solicitud como es obtener **"es la prevención o tratamiento de trastornos caracterizados por un aumento patológico de la resorción ósea"**, sería solucionado fácilmente por el experto en la materia con base en las composiciones farmacéuticas divulgadas en **D1** y **D2**, de manera que este lo lograría fácil y obviamente sin necesidad de emplear Habilidad Inventiva.

6. Conclusión:

Los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

N°	Documento	Título	Fecha de publicación
D1	US 6,143,326	"Oral pharmaceutical preparation containing ibandronat"	30/10/1997
D2	WO 00/21541	"Process for the preparation of oral pharmaceutical compositions comprising biphosphonates"	20/04/2000

7. Respuesta a los argumentos del solicitante:

- El solicitante modifica el objeto de la invención del empleo de los ácidos bifosfónicos a medicamento. El capítulo descriptivo en general se refiere al método de administración del medicamento.

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de 60 días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

DORIS ELENA POLO CÓRDOBA
Jefe de División de Nuevas Creaciones (E)
El anterior requerimiento fue notificado por fijación en lista, de fecha 27 FEB. 2009

CONCEPTO TÉCNICO No.0101	**EXAMINADOR TÉCNICO** Código No. 202070

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Señor
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 04-096462- -00009-0000
Fecha: 2009-05-27 16:46:01 Dep: 2020 NUECRLACIONI
Tra: 11 PATENTEIYII Eve: 379 FASENACIONALII
Act: 329 CTOINFORMACION Folios: 35

Re: P1.-**F.HOFFMANN-LA ROCHE AG**.-Solicitud de Patente de Invención en Fase Nacional PCT para "**ÁCIDO BISFOSFÓNICO PARA EL TRATAMIENTO Y PREVENCIÓN DE OSTEOPOROSIS**".-Clase **A61P 19/10**.-Expediente número **04-096.462.-**

1. Me refiero al auto dictado por ese Despacho notificado por fijación en lista el 27 de Febrero de 2009.

2. Con el fin de responder a las objeciones de nivel inventivo expuestas por el señor Examinador en el Concepto Técnico N° **101**, atentamente me permito presentar los siguientes argumentos técnicos y las siguientes modificaciones realizadas en el capítulo reivindicatorio de la solicitud, mediante lo cual se superan completamente dichas objeciones y se demuestra de manera contundente la patentabilidad de la presente invención.

3. **MODIFICACIONES AL CAPÍTULO REIVINDICATORIO**

En primer lugar me permito manifestar que el solicitante ha decidido modificar el capítulo reivindicatorio de la siguiente manera:

a) La reivindicación 1 ha sido restringida a un medicamento cuyo núcleo comprende 150 mg de ácido ibandrónico o una sal farmacéuticamente aceptable del mismo, junto con uno o más excipientes farmacéuticamente aceptables seleccionados entre lactosa, polivinilpirrolidona, celulosa microcristalina, crospovidona, ácido esteárico y dióxido de silicio, mientras que su recubrimiento comprende uno o más excipientes farmacéuticamente aceptables seleccionados entre el grupo conformado por hidroxipropil metilcelulosa, dióxido de titanio, talco y poli etilenglicol 6000;

b) De conformidad con el punto anterior, **las reivindicaciones 2 a 4 actualmente presentadas fueron eliminadas**; y finalmente

c) La nueva reivindicación 2, la cual corresponde básicamente a la reivindicación 5 actualmente presentada, se encuentra dirigida a especificar que la sal farmacéuticamente aceptable del ácido ibandrónico mencionado en la reivindicación 1 es la sal monosódica del ácido ibandrónico monohidrato.

De lo anterior es claro que las modificaciones realizadas en el capítulo reivindicatorio de la solicitud de patente en cuestión no amplían de manera alguna el alcance de la solicitud presentada originalmente, cumpliendo a cabalidad con las disposiciones de patentabilidad establecidas en el artículo 34 de la Decisión 486 de 2000.

4. ANÁLISIS DEL NIVEL INVENTIVO

Ahora bien, el señor Examinador objeta el nivel inventivo de la solicitud de patente en cuestión con base en las enseñanzas de los siguientes documentos:

D1 → US 6,143,326
D2 → WO 00/21541

En este sentido, el señor Examinador argumenta básicamente que el documento D1 divulga una formulación que comprende: i) un núcleo de tableta que contiene entre 0.1 a 100 mg de ibandronato y, 2) una cubierta libre de ibandronato que está compuesta por hidroxipropilmetilcelulosa, dióxido de titanio, poli etilenglicol y talco.

Asimismo, el señor Examinador señala que el documento D2 enseña un proceso para la preparación de composiciones farmacéuticas orales que comprenden bisfosfonatos, siendo la forma monohidrato del ibandronato sódico la sustancia activa preferida. A éste respecto, el señor Examinador resalta que en los ejemplos del documento D2 se enseñan formulaciones para tabletas que contienen lactosa, polivinilpirrolidona, celulosa microcristalina, crospovidona, ácido esteárico y dióxido de silicio.

Como consecuencia de lo anterior el señor Examinador concluye que un experto en la materia que se base en la información técnica previamente divulgada en las anterioridades D1 y D2 obtendría de manera evidente el medicamento revelado en la presente solicitud.

Ahora bien, en vista de lo anterior y con el ánimo de demostrar el inequívoco carácter inventivo de la presente invención con respecto a las enseñanzas de los documentos D1 y D2, inicialmente me permito presentar a ese Despacho un estudio detallado de las principales características técnicas del medicamento revelado por el solicitante, de manera que dicho estudio se convierta en el punto de partida para llevar a

cabo un análisis comparativo entre la información técnica revelada en la solicitud de patente en cuestión y las enseñanzas de las anterioridades D1 y D2.

4.1 Análisis técnico de la actividad farmacológica del medicamento revelado en la solicitud de patente en cuestión

En la presente solicitud se revela un medicamento para administración oral caracterizado porque es un comprimido recubierto por una película, en donde el núcleo del comprimido comprende:

- 150 mg de ácido ibandrónico o una sal farmacéuticamente aceptable del mismo; y

- uno o más excipientes farmacéuticamente aceptables seleccionados del grupo conformado por: lactosa, polivinilpirrolidona, celulosa microcristalina, crospovidona, ácido esteárico y dióxido de silicio;

y en donde el recubrimiento del comprimido comprende uno o más excipientes farmacéuticamente aceptables seleccionados entre el grupo conformado por: hidroxipropil metilcelulosa, dióxido de titanio, talco y poli etilenglicol 6000.

De acuerdo con estudios clínicos realizados[1,2], dicho medicamento presenta una actividad farmacológica que lo hace eficaz en la prevención y/o el tratamiento de trastornos que conducen al aumento patológico de la resorción ósea, tal como por ejemplo la osteoporosis, condición médica crónica que implica la pérdida de masa ósea.

La actividad farmacológica de los bisfosfonatos es conocida en el estado de la técnica (ver por ejemplo las patentes EP 170228 y WO 9000798). En efecto, dichos compuestos se caracterizan porque presentan una elevada afinidad por el fosfato de calcio y por ende, actúan como inhibidores de la resorción ósea.

Sin embargo, los bisfosfonatos se caracterizan porque irritan la piel y las membranas mucosas, por lo que al ser administrados por vía oral como parte de un tratamiento médico extendido ocasionan efectos secundarios en el tracto digestivo, tal como trastornos gastrointestinales. Lo anterior, sumado a la baja biodisponibilidad oral que presentan los bisfosfonatos hace que su administración oral resulte ser inconveniente.

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[1] ***Reginster et al.,*** *"Efficacy and tolerability of once-monthly oral ibandronate in postmenopausal osteoporosis: 2-year results from the MOBILE study" Ann. Rheum. Dis., 2006,* ***65****: 654-661. (Anexo iii)*

[2] ***E. Solomon;*** *"Ibandronate Treatment for Osteoporosis: Rationale, Preclinical, and Clinical Development of Extended Dosing Regimens"; Current Osteoporosis Reports; 2006;* ***4*** *(1); 14-20.(Anexo iv)*

De lo anterior es claro que en el estado de la técnica era necesaria una composición que permitiera eliminar los efectos secundarios generados por los ibandronatos sin que se viera alterada su actividad farmacológica como inhibidores de la resorción ósea.

Ahora bien, en respuesta a dicha necesidad la presente invención revela una novedosa composición que no solamente permite eliminar los problemas adversos relacionados con la administración recurrente de ibandronatos a pacientes que padecen problemas de osteoporosis, sino que de manera sorprendente muestra un aumento considerable en los efectos farmacológicos generados, toda vez que permite incrementar la densidad mineral ósea en los pacientes a los que se administra en un porcentaje mayor al que se logra por medio de las composiciones conocidas previamente en el estado de la técnica.

En efecto, el doctor Solomon Epstein[2] y el profesor Jean-Yves Reginster[1], entre otros, han publicado los resultados de un estudio clínico denominado MOBILE (sigla en inglés para la frase Monthly Oral iBandronate In LadiEs), el cual es un estudio de fase III diseñado para evaluar la eficacia y seguridad de diferentes composiciones que contienen ibandronatos.

Dicho estudio ha demostrado de forma contundente que una composición que comprende 150 mg de ácido ibandrónico (de conformidad con lo expuesto en el nuevo capítulo reivindicatorio de la solicitud en cuestión) genera un aumento sustancial en la densidad mineral ósea de la espina dorsal y el fémur proximal (que incluye cadera total, cuello femoral y trocánter del fémur) con respecto al incremento logrado mediante otras composiciones.

De manera específica, el estudio clínico MOBILE ha demostrado que la composición revelada en la presente invención permite obtener un aumento del 6,6% en la densidad mineral ósea de la espina lumbar luego de dos años de administración, mientras que una composición de administración diaria que comprende 2,5 mg de ibandronatos tan sólo permite lograr un aumento del 5,0%. Asimismo, la composición revelada permite lograr aumentos del 4,2%, 3,1% y 6,2% en la densidad mineral ósea de cadera, cuello femoral y trocánter del fémur, respectivamente, frente a aumentos del 3,1%, 2,2% y 4,6% logrados por la composición de administración diaria conocida en el estado de la técnica.

Adicional a lo anterior, también resulta de gran importancia resaltar que el estudio MOBILE ha permitido concluir que la composición revelada en la solicitud de patente en cuestión genera una drástica disminución de la concentración en plasma del marcador bioquímico de la resorción ósea denominado telopéptido C de colágeno tipo I (sCTX de acuerdo con sus siglas en inglés), toda vez que dicha novedosa composición permite disminuir los niveles de sCTX en un 67,7% luego de tres meses de administración, con

respecto a un 56,1% que es logrado a través de la composición de administración diaria conocida previamente en el estado de la técnica.

Lo planteado previamente demuestra que la composición de 150 mg de ácido ibandrónico revelada en la presente solicitud permite superar los efectos secundarios generados por los bisfosfonatos (esto como consecuencia de su administración mensual) y al mismo tiempo permite contrarrestar con mayor eficacia las implicaciones físicas de la resorción ósea, esto es, permite disminuir en mayor porcentaje las pérdidas de masa ósea generadas por condiciones médicas como la osteoporosis.

Ahora bien, teniendo en cuenta lo anterior me permito presentar a continuación un análisis comparativo entre la información técnica revelada en la solicitud de patente en cuestión y las enseñanzas de las anterioridades D1 y D2.

4.2 Consideraciones con respecto a los documentos US 6,143,326 (D1) y WO 00/21541 (D2)

En términos generales, el documento **D1** enseña composiciones farmacéuticas para aplicación oral que contienen ibandronato o una sal fisiológicamente tolerable del mismo.

Específicamente, y de acuerdo con lo establecido por los autores de dicho documento, las formulaciones sólidas enseñadas en **D1** comprenden: a) un núcleo que contiene entre 0.1 mg y 100 mg de ibandronato; y, b) un recubrimiento conformado por hidroxipropilmetilcelulosa, poli etilenglicol, dióxido de titanio y talco, es decir, un recubrimiento que está libre de ingrediente activo pero que se caracteriza por permitir que éste último sea liberado rápidamente.

Por su parte, el documento **D2** enseña un proceso para la preparación de composiciones farmacéuticas que contienen bisfosfonatos, el cual está caracterizado básicamente porque la sustancia activa es inicialmente granulada en húmedo por medio de un granulador de lecho fluidizado junto con adyuvantes que no presentan acción abrasiva, y posteriormente es secada, tamizada y procesada para obtener las composiciones farmacéuticas requeridas.

En conexión con lo anterior, resulta de gran importancia resaltar que el objetivo principal de dicha anterioridad era desarrollar un proceso que permitiera reducir las pérdidas de sustancia activa durante el proceso de preparación de composiciones farmacéuticas que contienen no más de 50 mg de bisfosfonatos por unidad de dosis.

De conformidad con lo anterior, en los ejemplos 1, 2 y 3 del documento **D2** se describen los procesos utilizados para obtener cápsulas que contienen 1,0 mg ó 2,5 mg

de ibandronato sódico mezclados con excipientes tales como lactosa, polivinilpirrolidona, polivinilpirrolidona reticulada, ácido esteárico, celulosa microcristalina y SiO_2 coloidal.

Ahora bien, de acuerdo con el señor Examinador una persona medianamente versada en la materia habría podido obtener el medicamento revelado en la presente solicitud de manera obvia a partir de la combinación de las enseñanzas de los documentos D1 y D2, por lo que concluye que dicha solicitud carece de nivel inventivo.

De manera específica, los argumentos dados por el señor Examinador en su Concepto Técnico para sustentar dicha conclusión consisten en que D1 enseña composiciones cuyo núcleo comprende entre 0,1 a 100 mg de ibandronato y cuyo recubrimiento está conformado por hidroxipropilmetilcelulosa, poli etilenglicol, dióxido de titanio y talco, mientras que D2 enseña cápsulas que comprenden ibandronato mezclado con excipientes como lactosa, polivinilpirrolidona, polivinilpirrolidona reticulada, ácido esteárico, celulosa microcristalina y SiO_2 coloidal.

En respuesta a lo anterior me permito manifestar que, -contrario a lo afirmado por el señor Examinador-, la materia técnica revelada en la solicitud de patente en cuestión sí presenta un inequívoco carácter inventivo con respecto a las enseñanzas de los documentos D1 y D2, toda vez que durante el análisis de patentabilidad realizado por ese Despacho de ninguna manera se han tenido en cuenta las siguientes consideraciones técnicas:

a) En primer lugar, si bien la persona medianamente versada en la materia encuentra en los documentos D1 y D2 información técnica que le sugiere los excipientes que conforman el núcleo y el recubrimiento del comprimido revelado en la presente invención, dichas anterioridades de ninguna manera enseñan o sugieren una composición que contiene 150 mg de ácido ibandrónico, esto es, no enseñan y tampoco sugieren una composición que comprende el 200% de la dosis conocida previamente en el estado de la técnica para tratar los efectos de la resorción ósea.

   De conformidad con lo anterior me permito plantear el siguiente interrogante:

   ¿Con base en las enseñanzas del arte previo y teniendo en cuenta el objetivo de solucionar los problemas gastrointestinales asociados con el consumo de compuestos bisfosfonatos, por qué una persona sugeriría una composición que comprende 150 mg de ácido ibandrónico, es decir, una composición que comprende el 200% de la dosis conocida en el arte previo para tratar los efectos de la resorción ósea?

En respuesta a lo anterior y de acuerdo con lo planteado previamente en el presente memorial me permito señalar que dicha persona únicamente sugeriría tal composición como resultado de un trabajo inventivo, el cual, tal como se analiza en el siguiente punto, permite lograr un avance significativo en el estado de la técnica.

b) Los documentos D1 y D2 enseñan composiciones que contienen ibandronatos, así como su proceso de producción. Sin embargo, dichas anterioridades no le indican a una persona medianamente versada en la materia que una composición que comprende 150 mg de ácido ibandrónico permite obtener un aumento en la densidad mineral de la espina dorsal y el fémur proximal (que incluye cadera total, cuello femoral y trocánter del fémur) con respecto al incremento logrado mediante otras composiciones.

En este sentido, es claro que en los documentos D1 y D2 no existe ninguna indicación técnica que sugiera que una composición que comprende 150 mg de ácido ibandrónico permite eliminar los inconvenientes gastrointestinales provocados por los bisfosfonatos y al mismo tiempo permite *no solamente* mantener la actividad farmacológica relacionada con la prevención y/o el tratamiento de trastornos que conducen al aumento patológico de la resorción ósea, sino que permite disminuir en mayor porcentaje las pérdidas de masa ósea generadas por condiciones médicas como la osteoporosis.

Ahora bien, aparte de lo anterior considero de gran importancia señalar que el Manual Andino de Patentes[3] plantea el *método problema – solución* como un mecanismo para determinar si el objeto de una solicitud resulta obvio o se deriva de manera evidente del estado de la técnica. De acuerdo con dicho método, el Examinador debe plantearse los siguientes interrogantes, teniendo en cuenta que sólo si la respuesta es afirmativa en todos los casos la solicitud bajo estudio carece de nivel inventivo:

1. ¿Estaba un técnico con conocimientos medios en la materia en condiciones de plantearse el problema?

2. ¿De resolverlo en la forma en que se reivindica?

3. ¿De prever el resultado?

Para el caso en cuestión es claro que en el estado de la técnica eran conocidos los efectos secundarios de los bisfosfonatos, razón por la cual puede considerarse que una persona medianamente versada en la materia sí estaba en condiciones de plantearse el problema.

[3] **SECRETARÍA GENERAL DE LA COMUNIDAD ANDINA**; Manual Andino para el examen de solicitudes de patentes de invención en las Oficinas de Propiedad Industrial de los Países de la Comunidad Andina; Lima, Perú: 2004. Páginas 77 y 78.

Sin embargo, tal y como se analizó anteriormente en el presente escrito, una persona medianamente versada en la materia no encuentra en los documentos que conforman el arte previo ninguna indicación técnica que le sugiera una composición que comprenda una cantidad de ácido ibandrónico correspondiente al 200% de la dosis conocida en el estado de la técnica anterior para tratar los efectos de la resorción ósea, así como tampoco encuentra ninguna indicación técnica que lo lleve a predecir que dicha novedosa composición permite incrementar la densidad mineral ósea en los pacientes a los que se administra en un porcentaje mayor al que se logra por medio de las composiciones conocidas previamente en el estado de la técnica.

Por lo tanto, es claro que para el caso en cuestión la respuesta a las preguntas 2 y 3 del método problema – solución es negativa, con lo cual se concluye que el nivel inventivo de las composiciones reveladas en la presente invención debe ser reconocido.

Finalmente, en vista de lo planteado previamente en el presente memorial me permito señalar una vez más ante ese Despacho que la materia técnica revelada en la solicitud de patente en cuestión presenta un inequívoco carácter inventivo con respecto a las enseñanzas de los documentos D1, D2 ó la combinación de ambos, cumpliendo a cabalidad con las disposiciones de patentabilidad establecidas en el artículo 18 de la Decisión 486 de 2000.

5. **CONCLUSIÓN**

De conformidad con las modificaciones realizadas en el capítulo reivindicatorio de la solicitud de patente en cuestión, así como teniendo en cuenta los argumentos técnicos presentados para demostrar el inequívoco carácter inventivo que presenta la novedosa composición farmacéutica revelada por el solicitante y el sorprendente aporte al estado de la técnica proporcionado, es completamente claro que se han superado las objeciones expuestas por el señor Examinador, y por lo tanto, dicha solicitud es merecedora del privilegio de patente solicitado.

6. Anexo al presente memorial me permito presentar:

(i) Copia del nuevo capítulo reivindicatorio, el cual está compuesto por 2 reivindicaciones y reemplaza al actualmente presentado;

(ii) Copia del artículo "*Reginster et al., Ann Rheum Dis., 2006, **65**: 654-661.*"; *y*

*(iii) E. Solomon; "Ibandronate Treatment for Osteoporosis: Rationale, Preclinical, and Clinical Development of Extended Dosing Regimens"; Current Osteoporosis Reports; 2006; **4** (1); 14-20.*

7. En vista de lo anterior, ruego a usted proceder a estudiar nuevamente la solicitud a la luz de los argumentos presentados y conceder el privilegio de patente solicitado.

Señor Superintendente,

ALICIA LLOREDA RICAURTE
T.P. 53.215

NOTARIA 41 DEL CIRCULO DE BOGOTA D.C.
DEPARTAMENTO DE CUNDINAMARCA
REPUBLICA DE COLOMBIA

El Notario 41 del círculo de Bogotá D.C. declara que el presente escrito fue presentado personalmente por: Alicia Lloreda Ricaurte identificada (o) con C.C. 39.690.713 y Tarjeta profesional de abogado No. 53.215 del Consejo Superior de la Judicatura, quien autentica la firma puesta por ella (el) mismo en este escrito.
(Art. 84 C. P. C. Decreto 2282/89 mod. 89)

11 MAYO 2009

Bogotá D.C.

ALICIA LLOREDA RICAURTE
C.C. No. 39.690.713 de Usaquén

REIVINDICACIONES

1. Un medicamento para administración oral caracterizado porque es un comprimido recubierto por una película, en donde el núcleo del comprimido comprende:

- 150 mg de ácido ibandrónico o una sal farmcéuticamente aceptable del mismo; y,
- uno o más excipientes farmacéuticamente aceptables seleccionados del grupo conformado por: lactosa, polivinilpirrolidona, celulosa microcristalina, crospovidona, ácido esteárico y dióxido de silicio;

y en donde el recubrimiento del comprimido comprende uno o más excipientes farmacéuticamente aceptables seleccionados entre el grupo conformado por: hidroxipropil metilcelulosa, dióxido de titanio, talco y polietilenglicol 6000.

2. El medicamento de acuerdo con la reivindicación 1, en donde la sal farmacéuticamente aceptable del ácido ibandrónico es la sal monosódica del ácido ibandrónico monohidrato.

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Efficacy and tolerability of once-monthly oral ibandronate in postmenopausal osteoporosis: 2-year results from the MOBILE study

J-Y Reginster, Silvano Adami, Peter Lakatos, Maria Grennwald, Jan J Stepan, Stuart L Silverman, Claus Christiansen, Lucy Rowell, Nicole Mairon, Bernard Bonvoisin, Marc K Drezner, Ronald Emkey, Dieter Felsenberg, Cyrus Cooper, Pierre D Delmas and Paul D Miller

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Extended report

Efficacy and tolerability of once-monthly oral ibandronate in postmenopausal osteoporosis: 2-year results from the MOBILE study

J-Y Reginster, S Adami, P Lakatos, M Greenwald, J J Stepan, S L Silverman, C Christiansen, L Rowell, N Mairon, B Bonvoisin, M K Drezner, R Emkey, D Felsenberg, C Cooper, P D Delmas, P D Miller

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Keywords: monthly, ibandronate, osteoporosis, bisphosphonate, non-inferiority

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Background: Reducing bisphosphonate dosing frequency may improve suboptimal treatment adherence and therefore therapeutic outcomes in postmenopausal osteoporosis. Once-monthly oral ibandronate has been developed to address this issue.
Objective: This 2-year analysis was performed to confirm the 1-year results and provide more extensive safety and tolerability information for once-monthly dosing.
Methods: MOBILE, a randomised, phase III, non-inferiority study, compared the efficacy and safety of once-monthly ibandronate with daily ibandronate, which has previously demonstrated vertebral fracture risk reduction versus placebo.
Results: 1609 postmenopausal women were randomised. Substantial increases in lumbar spine bone mineral density (BMD) were observed in all arms: 5.0%, 5.3%, 5.6% and 6.6% in the daily and once-monthly groups (50 + 50 mg, 100 mg and 150 mg), respectively. All once-monthly regimens were confirmed at least as effective as daily, and in addition 150 mg was proven superior ($p<0.001$). Substantial increases in proximal femur BMD (total hip, femoral neck, trochanter) were observed; 150 mg produced the most pronounced effect ($p<0.05$ versus daily). Independent of the regimen, most participants (70.5–93.5%) achieved increases above baseline in lumbar spine or total hip BMD or both. Pronounced decreases in the biochemical marker of bone resorption, sCTX, observed in all arms after 3 months, were maintained throughout. The 150 mg regimen consistently produced greater increases in BMD and sCTX suppression than the 100 mg and daily regimens. Ibandronate was well-tolerated, with a similar incidence of adverse events across groups.
Conclusions: Once-monthly oral ibandronate is at least as effective and well-tolerated as daily. Once-monthly administration may further improve patient convenience and therapeutic adherence, thereby optimising outcomes.

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Osteoporosis is a chronic, age-related condition. Bone loss occurs without presenting symptoms and is often only diagnosed as a result of a related fracture. An estimated one in three women will sustain an osteoporosis-related fracture in their lifetime.[1] These fractures result in increased disability and excess mortality. In 2003, the estimated total direct cost of osteoporosis-related fractures in the European Union during the first year post-fracture was €25 billion.[2] In the USA, the annual expenditure for care of osteoporotic fractures was estimated to be $17.5 billion in 2002 (adjusted from 1995 to 2002 dollars).[3]

Oral bisphosphonates produce clinically significant reductions in the risk of new vertebral fractures[4–8] and are the current mainstay of treatment for postmenopausal osteoporosis. However, long-term treatment is required for optimal and sustained benefit.[9 10] Long-term adherence to any therapy, regardless of the disease, is known to be poor.[11] Based on evidence from other chronic diseases,[12] it is expected that reducing the burden of administration by further decreasing the dosing frequency of bisphosphonates may improve adherence.[13] This is seen in the significant advantage provided by weekly over daily dosing.[14–16] However, a growing body of evidence suggests that real-world adherence with weekly oral bisphosphonates remains suboptimal. Indeed, recent studies suggest that persistence rates with weekly bisphosphonates at 1-year are less than 50%.[14–16] Poor therapeutic adherence results in: smaller decreases in bone turnover, reduced bone mineral density (BMD) gains and a greater risk of fractures.[17–19]

Ibandronate (Bonviva) is a potent, nitrogen-containing bisphosphonate that can be administered with extended between-dose intervals.[20 21] Ibandronate is approved for the treatment of postmenopausal osteoporosis based on its demonstration of significant vertebral antifracture efficacy when administered orally, either daily or intermittently with an extended between-dose interval of >2 months, with a safety and tolerability profile similar to placebo.[4 5] A dose-response relationship has been demonstrated with once-monthly oral ibandronate, in a randomised, double-blind, dose-finding, phase I study (Monthly Oral Pilot Study: MOPS), for systemic exposure (area under the curve and maximum concentration) and reduction of bone resorption;[22] confirming the feasibility of once-monthly oral ibandronate dosing.

On the basis of these positive studies, MOBILE (Monthly Oral iBandronate In LadiEs) a randomised, phase III, non-inferiority study was initiated. MOBILE was designed to compare the efficacy and safety of three once-monthly oral ibandronate regimens (50 + 50 mg (given on 2 consecutive days), 100 mg and 150 mg) with the efficacious and well-tolerated daily oral ibandronate regimen (2.5 mg).[4 5] The 1-year results indicated that all of the once-monthly ibandronate regimens were at least as effective as the active comparator, daily ibandronate, producing substantial increases in lumbar spine and proximal femur (total hip, femoral neck and trochanter) BMD.[23] Furthermore, the once-monthly regimens had a tolerability profile similar to the daily regimen. The 1-year analysis also suggested a more pronounced effect for all efficacy endpoints with the 150 mg once-monthly regimen versus the 2.5 mg daily and 100 mg once-monthly regimens, with similar safety and tolerability.

The purpose of this prospective, 2-year analysis was to confirm the findings of the 1-year efficacy analysis and to provide more extensive safety and tolerability information for once-monthly ibandronate dosing.

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PATIENTS AND METHODS

Study design

MOBILE was a 2-year, randomised, double-blind, parallel-group, phase III, non-inferiority study, conducted in 65 centres in USA, Canada, Mexico, Brazil, Europe, Australia and South Africa. The Institutional Review Boards of the participating centres provided ethical approval of the study. The study was conducted in accordance with the principles of the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice guidelines.

Study participants and medication

All study participants were ambulatory postmenopausal women, aged 55–80 years and at least 5 years since menopause, with osteoporosis (mean lumbar spine (L2–4) BMD T-score between <–2.5 and >–5.0). Further details of the pre-specified inclusion and exclusion criteria have previously been reported.[23] All participants provided written informed consent.

At enrolment, participants were randomised into one of four oral ibandronate treatment groups, either 2.5 mg daily, 50 + 50mg once-monthly (single doses given on 2 consecutive days), 100 mg once-monthly or 150 mg once-monthly. Participants also received daily or once-monthly oral placebo to maintain blinding, plus daily elemental calcium (500 mg) and vitamin D (400 IU) supplements. Participants were instructed to take their study medication following an overnight fast (≥6 hours) and with 240 ml (8oz) of plain water. They were then required to stay upright and fast for at least 60 minutes after dosing.

Primary efficacy endpoint

The primary efficacy endpoint was the change (%) from baseline in lumbar spine (L2–4) BMD at 1 year, as measured by dual-energy X-ray absorptiometry (DXA). The results for the primary efficacy endpoint have previously been reported.[23]

Secondary efficacy endpoints

Secondary efficacy endpoints included the change (%) from baseline in lumbar spine (L2–4) and proximal femur (total hip, femoral neck, hip trochanter) BMD at 2 years, as measured by DXA. GE Lunar (Madison, WI, USA) or Hologic (Bedford, MA, USA) instruments were used when performing DXA scans; scans were assessed by a central BMD reading centre (Synarc, Portland, USA). Responder analyses, defined as the percentage of participants maintaining or achieving increases in lumbar spine BMD, total hip BMD or lumbar spine *and* total hip BMD above baseline were performed. In addition, the proportion of patients achieving defined increases in lumbar spine or total hip BMD (≥6% and ≥3%, respectively), previously associated with vertebral[24] and non-vertebral[25] antifracture efficacy, was also prospectively evaluated.

The change (%) from baseline in serum concentrations of the biochemical marker of bone resorption C-telopeptide of the α-chain of type I collagen (sCTX) was also measured at 2 years. Blood samples for sCTX assessments were taken immediately before the next scheduled, once-monthly dose, after an overnight fast (≥6 hours), and between 8.00am and 10.00am. sCTX levels measured in the once-monthly groups therefore represent the residual magnitude of suppression at the end of the dosing interval. sCTX assays (Elecsys β-CrossLaps/serum, Elecsys 2010, Roche Diagnostic, Basel, Switzerland) were analysed at a central biomarker laboratory (Synarc, Lyon, France). The proportion of patients responding to treatment with sCTX reductions of ≥50% and ≥70% from baseline was also prospectively identified. The threshold of 50% corresponds with the least significant change (1.96 x square root of 2 x CV).[26]

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Safety parameters
Adverse events were continuously monitored throughout the study. The relationship to treatment and intensity of all adverse events was also assessed. Clinical vertebral and non-vertebral fractures were identified symptomatically, confirmed radiographically and reported as adverse events. Laboratory safety parameters were analysed at baseline and every 6 months thereafter. Samples were processed at a centralised safety laboratory (MDS, Les Ponts de Baillet, France).

Randomisation
Eligible patients were stratified by centre and baseline BMD status prior to randomisation, to ensure comparable distribution of baseline BMD across the treatment arms. Participants were randomised using adaptive minimisation via a centralised 'call in' system (Interactive Voice Response System, ClinPhone Ltd, Nottingham, UK).

Statistical analysis
Analysis populations
The per-protocol (PP) population was used as the primary analysis population for all efficacy parameters as this is considered the most conservative approach to detecting actual differences among treatments when performing a non-inferiority analysis.[27] The PP population consisted of all those participants in the intent-to-treat (ITT) population who had no major protocol violations at baseline or during the first year of study. Major violations were categorised as: a baseline lumbar spine (L2–4) BMD T-score >–2.5; poor compliance with treatment; unconfirmed menopausal status; prohibited concomitant disease or treatment prior to study; lack of efficacy data or reliable BMD data. If such violations occurred during year 2 then data from individual visits were censored rather than the patient being completely excluded from the analysis.

The ITT population included all participants who were randomised, received at least one dose of study medication and had at least one efficacy follow-up data point. To confirm the robustness of the PP findings, analyses were also performed for all efficacy endpoints using the ITT population. The safety population included all participants who received at least one dose of study medication, including withdrawn participants, and had at least one follow-up assessment.

Analysis of primary efficacy parameter at 2 years and secondary efficacy endpoints
At 2 years, the change (%) from baseline in lumbar spine BMD with the once-monthly regimens was compared with the daily regimen using a non-inferiority test. Non-inferiority margins for the analysis of change (%) from baseline in lumbar spine BMD were based on 30% of the minimum treatment effect observed between daily oral ibandronate and placebo after 2 years in a prior clinical study (BONE).[4] On this basis, non-inferiority could be concluded if the lower boundary of the two-sided 95% CI for the difference in the means between the once-monthly and daily regimens was ≥–1.3% at 2 years.

If non-inferiority was demonstrated for the primary efficacy parameter then superiority of the once-monthly regimens to the daily regimen would be tested using analysis of variance, controlling for geographic location and baseline BMD. Changes (%) from baseline in proximal femur BMD and sCTX were summarised only, with 95% CIs for the difference in the mean BMD and median sCTX values between the once-monthly and daily regimens calculated. The percentage of participants responding to treatment was compared using a chi-squared test.

Analysis of safety variables
All adverse events reported throughout the 2-year study period were included in the safety analysis. All of the observed adverse events were evaluated, on a per patient basis, by standardised tabulation of the frequency and incidence rates.

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RESULTS

Patient disposition and baseline characteristics

In accordance with the original sample size calculation,[23] 1609 postmenopausal women were randomised into the study. Patient disposition is summarized in figure 1. A total of 1291 participants completed 2 years of treatment, with 292 (18.1%) participants withdrawing from the study. The majority of patients withdrew from the study during the first 3 months, regardless of treatment group.

The number of participants included in the PP population was 1277; the main reasons for excluding patients from the PP population, based upon 1-year data, were: non-compliance with daily or monthly schedule (~17%), and no reliable BMD values (~6%). Data were also censored for non-compliance with daily study medication (~8%) or the monthly dosing schedule during year 2 (~7%). The number of participants included in the ITT population was 1572. Since, all patients took both daily and monthly tablets, these measures of compliance do not allow conclusions on differences in therapeutic adherence.

Baseline patient characteristics, such as age, years since menopause, history of fractures, bone turnover markers and lumbar spine BMD, were well balanced across the treatment groups (table 1).

Table 1 Demographics (safety population; mean)

	2.5 mg (n = 395)	50 + 50 mg (n = 396)	100 mg (n = 396)	150 mg (n = 396)
Age (years)	65.8	66.0	66.2	66.2
Weight (kg)	64.1	64.1	64.0	63.7
Height (cm)	157.1	157.4	157.3	158.0
Body mass index (kg/m^2)	25.9	25.8	25.9	25.5
Time since menopause (years)	18.3	18.7	19.1	18.3
History of previous fractures (%)*	48.9	46.3	45.5	47.0
Lumbar spine (L2–L4) BMD (g/cm^2)	0.755	0.755	0.756	0.754
Lumbar spine (L2–L4) BMD (T –score)	–3.28	–3.28	–3.27	–3.28
sCTX (ng/ml)†	0.49	0.52	0.51	0.50
25-OH-D (ng/ml)	25.7	24.4	25.1	24.7

*% of patients.
†Median value

Efficacy analysis

Substantial increases in lumbar spine (L2–4) BMD were observed in all treatment arms (fig 2). Compared with baseline, mean increases in lumbar spine BMD were 5.3% (95% CI: 4.8, 5.9), 5.6% (95% CI: 5.1, 6.1) and 6.6% (95% CI: 6.0, 7.1) in the 50 + 50 mg, 100 mg and 150 mg once-monthly groups, respectively, compared with 5.0% (95% CI: 4.4, 5.5) in the daily group. All once-monthly regimens were prospectively proven non-inferior, and thus shown to be at least as effective as the daily regimen (fig 3). Furthermore, 150 mg once-monthly was prospectively proven superior to the daily regimen ($p<0.001$). A post-hoc analysis showed that, for mean increase in lumbar spine (L2–4) BMD, the 150 mg once-monthly ibandronate group was also statistically superior to the 100 mg once-monthly group ($p=0.011$).

The ITT analysis confirmed these findings; mean increases in lumbar spine (L2–4) BMD were 5.3% (95% CI: 4.7, 5.8), 5.3% (95% CI: 4.8, 5.8) and 6.4% (95% CI: 5.9, 6.9) in the 50 + 50 mg, 100 mg and 150 mg once-monthly groups, respectively, compared with 4.8% (95% CI:

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4.3, 5.3) in the daily group. All of the once-monthly regimens were non-inferior to the daily regimen, and the 150 mg once-monthly regimen was superior ($p<0.001$). The 150 mg once-monthly ibandronate group was also found, by post-hoc analysis, to be statistically superior to the 100mg group for mean increases in lumbar spine (L2–4) BMD ($p=0.003$).

Large increases in proximal femur BMD (total hip, trochanter and femoral neck) were also observed in all treatment arms (fig 2). As at the lumbar spine, the most substantial increases in hip BMD were observed with the 150 mg regimen. From the 95% CIs for the difference between the means associated with the 100 mg and 150 mg regimens compared with the daily regimen, it was concluded that both regimens produced superior increases in total hip, femoral neck and trochanter BMD ($p<0.05$) (fig 2). Comparable findings were obtained from the ITT analysis with substantial increases in proximal femur BMD reported for all ibandronate treatment regimens. The results of the superiority analysis were replicated with the ITT population, the one exception being the 100 mg regimen, which was not superior to the daily regimen for increases in femoral neck BMD.

Independent of the ibandronate dosing regimen, lumbar spine BMD, total hip BMD or both increased above baseline in most participants (70.5–93.5%) (fig 4). In the 150 mg once-monthly oral ibandronate group response rates at 2 years were consistently over 87% for increases in lumbar spine or total hip BMD above baseline, and were significantly greater compared with the daily treatment group ($p\leq0.004$). A post-hoc analysis found the incidence of responders with increases above baseline in lumbar spine BMD or lumbar spine *and* total hip BMD in the 150 mg once-monthly treatment group to be significantly greater than in the 100 mg once-monthly treatment group ($p<0.01$).

Large proportions of patients also achieved target increases in lumbar spine (≥6%; 35.4–54.3%) or total hip (≥3%; 40.4–65.1%) BMD (fig 4). Overall, larger proportions of patients in the once-monthly treatment arms achieved target increases in BMD compared with the daily arm, with the highest responder rates consistently observed with the 150 mg regimen ($p<0.05$ versus daily for all responder analyses; fig 4).

The incidence of responders to treatment was similar in the ITT analysis population; the 150 mg once-monthly treatment group had a statistically significant increase in the percentage of patients with lumbar spine BMD, total hip BMD or both above baseline and with target increases (lumbar spine ≥6%, and total hip ≥3%) compared with the 2.5 mg daily treatment group ($p\leq0.01$).

In all of the treatment arms, the pronounced decreases in sCTX observed after 3 months[23] were maintained throughout the 2-year study period (fig 5). Compared with baseline, median sCTX levels decreased by 56.1%, 60.5% and 67.7% in the 50 + 50 mg, 100 mg and 150 mg arms, respectively, compared with 61.5% in the daily group at 2 years.

The percentage of patients with a ≥50% decrease in sCTX from baseline was greater in the 150 mg once-monthly treatment group (78.7%), than in the 50 + 50 mg (60.9%), 100 mg (63.5%) and the 2.5 mg daily groups (65.6%, $p=0.002$). The proportion of patients with a ≥70% decrease in sCTX from baseline follows the same pattern: 35.3%, 27.0%, 35.1% and 48.1% for the 2.5 mg, 50 + 50 mg, 100 mg and 150 mg treatment groups respectively. A significantly greater proportion of patients responded to the 150mg once-monthly regimen compared with the daily regimen ($p=0.006$). The ITT population analysis found comparable results for both levels of sCTX suppression.

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Safety parameters

A similar proportion of patients in the once-monthly and daily arms withdrew from treatment. The numbers of withdrawals (not including deaths) due to adverse events were evenly balanced across the treatment arms: 31 (8%), 42 (11%), 36 (9%) and 39 (10%) in the 50 + 50 mg, 100 mg, 150 mg and daily groups, respectively (fig 1).

The incidence of adverse events, drug-related adverse events and drug-related adverse events leading to withdrawal was well-balanced across the treatment arms (table 2). The most commonly reported adverse events, irrespective of relationship to treatment, were hypertension, dyspepsia and arthralgia; occurring with similar frequency across the treatment groups, and consistent with the population under study. A low rate of serious adverse events was observed. Only eight treatment-related serious adverse events were reported during the 2-year study period. These were: gastric ulcer (two cases), duodenal ulcer, erosive duodenitis, gastric ulcer haemorrhage, gastritis haemorrhagic, melaena and liver disorder. Most adverse events were considered unrelated to treatment and resulted in only a small number of patient withdrawals (table 2). In total, six deaths occurred during the study period, two during the second year, all of which were unrelated to treatment.

Table 2 Overall summary of safety (safety population; n [%])

	2.5 mg (n = 395)	50 + 50 mg (n = 396)	100 mg (n = 396)	150 mg (n = 396)
Overall				
Any adverse event	302 (76.5)	313 (79.0)	318 (80.3)	317 (80.1)
Any drug-related adverse event	128 (32.4)	119 (30.1)	143 (36.1)	146 (36.9)
Any drug-related adverse event leading to withdrawal	30 (7.6)	20 (5.1)	26 (6.6)	27 (6.8)
Any serious adverse event	38 (9.6)	54 (13.6)	55 (13.9)	45 (11.4)
Any drug-related serious adverse event	2 (0.5)	2 (0.5)	3 (0.8)	1 (0.3)
Any drug-related serious adverse event leading to withdrawal	1 (0.3)	1 (0.3)	0	1 (0.3)
Adverse events of special interest				
Upper GI adverse events	90 (22.8)	79 (19.9)	102 (25.8)	89 (22.5)
Clinical osteoporotic fractures	24 (6.1)	29 (7.3)	24 (6.1)	27 (6.8)

The incidence of upper gastrointestinal (GI) adverse events was similar across the treatment arms (20–26%; table 2) and events were generally mild to moderate in severity. The number of participants reporting upper GI events was slightly increased when considering only those that were taking nonsteroidal anti-inflammatory drugs (NSAIDs) and/or aspirin at baseline (23.6–31.2%). However, the incidence of upper GI events was well balanced across the once-monthly and daily arms. In particular, there was no evidence that treatment for 2 years with once-monthly doses of 150 mg led to an increased incidence in upper GI adverse events compared with the other once-monthly or daily treatment groups.

The number of patients with diagnosed flu-like illness considered by the investigator to be possibly or probably related to treatment was 1 (0.3%), 4 (1.0%), 5 (1.3%) and 13 (3.3%) for the 2.5 mg, 50 + 50mg, 100 mg and 150 mg groups, respectively. Such events were typically of short duration (1–4 days), mild to moderate in intensity and associated with the first administered dose only. None of the patients experiencing flu-like illness during year 1 had a recurrence of symptoms during year 2 of the study.

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The number of clinical osteoporotic fractures was similarly low across the treatment groups (table 2). Overall, there were no clinically relevant changes in the mean haematology or clinical chemistry values during treatment in either the daily or monthly treatment groups.

DISCUSSION

MOBILE is a randomised, double-blind, comparative, non-inferiority trial with the primary efficacy endpoint defined as the change (%) from baseline in lumbar spine BMD after 1 year.[23] The data were analysed at 2-years to confirm the 1-year efficacy and safety findings, and to provide more extensive information regarding once-monthly oral ibandronate for use in the treatment of postmenopausal osteoporosis.

The 2-year analysis categorically confirms the findings and conclusions drawn from the 1-year result.[23] All of the once-monthly regimens produced substantial increases in lumbar spine BMD and were shown by non-inferiority test to be at least as effective as the daily oral ibandronate regimen at 1 and 2 years. As at 1 year, the increases in lumbar spine BMD observed in the 150 mg treatment arm were prospectively proven to be superior to the daily regimen ($p<0.001$).

In addition to spinal BMD, the once-monthly regimens produced significant increases in proximal femur BMD (total hip, femoral neck and trochanter) by the end of the 2-year study period, with the greatest gains observed with the 150 mg regimen ($p<0.05$). The 150 mg once-monthly regimen consistently produced substantial improvements in proximal femur BMD over and above those observed with the daily regimen.

The increases in BMD are further supported by the marked decreases in sCTX observed in all treatment regimens. Pronounced decreases in sCTX were observed as early as 3 months[23] and were maintained throughout the 2-year study period.

The pre-specified responder analyses consistently demonstrated that a significantly larger proportion of postmenopausal women receiving 150 mg once-monthly ibandronate achieve increases in lumbar spine and/or total hip BMD and decreases in sCTX of a defined magnitude after 2 years compared with the daily regimen. This is particularly important considering that increases in vertebral BMD and decreases of biochemical markers of bone are both independently predictive for antifracture efficacy.[24 25 28]

Following the second year of therapy, the safety profile of the daily and once-monthly regimens was demonstrated to be favourable and consistent with that reported after 1 year.[23] All ibandronate regimens were generally well-tolerated, with a similar incidence of adverse events and serious adverse events across the treatment groups. No upper GI safety and tolerability concerns were identified; the incidence rates were low and comparable across the once-monthly and daily treatment arms, and no clinically relevant imbalances were observed even in patients receiving concomitant NSAIDs and/or aspirin. The 2-year results furthermore confirmed a low incidence of flu-like illness, of similar magnitude to that observed with other oral bisphosphonates,[29 30] with events being of short duration and most frequently associated with the initial administration only. Overall, no relevant differences in safety and tolerability were observed between the once-monthly and daily regimens. The findings of the overall safety and tolerability analysis are fully aligned with the favourable profile for oral ibandronate observed in prior clinical studies, in which a safety profile similar to placebo was observed, independent of the dosing regimen.[4]

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For all efficacy endpoints, the 150 mg once-monthly regimen provides additional benefits versus the daily and 100 mg once-monthly regimens, without compromising safety and tolerability. A relative risk reduction in the incidence of new vertebral fractures of 62%, associated with significant increases in lumbar spine and suppression of bone turnover markers, has been demonstrated for daily oral ibandronate.[4 5] The 150 mg once-monthly regimen studied in MOBILE provided marked gains in lumbar spine BMD and decreases in sCTX over and above those demonstrated with the daily oral regimen.

A once-monthly oral ibandronate regimen may provide further benefits through potentially greater treatment adherence. The recently reported strong patient preference for a once-monthly bisphosphonate dosing regimen[13] is expected to translate into improved therapeutic adherence and suggests that once-monthly ibandronate dosing could provide additional adherence benefits over current dosing strategies, such as weekly. Improved adherence with once-monthly ibandronate may translate into enhanced outcomes. Once-monthly ibandronate is likely to provide an effective and patient-friendly treatment option in postmenopausal osteoporosis.

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Attending symposia: J-YR, SA, JJS, MKD, CCo, DF, PDD
Giving lectures: J-YR, SA, MG, SLS, MKD, RE, CCo, DF, PDD
Funds for a member of staff: JJS
Organising educational programmes: DF.
LR, NM, BB are employees of F. Hoffmann-La Roche Ltd.
PL has no competing interests.

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FIGURE LEGENDS

Figure 1 Patient disposition.

Figure 2 Change (%) from baseline in lumbar spine and proximal femur BMD at 2 years (PP; mean [95% CI]).

Figure 3 Forest plot of the difference in the means (95% CI) of the mean change (%) from baseline in lumbar spine (L2–4) BMD between the once-monthly and daily oral ibandronate regimens after 2 years (PP), demonstrating that all once-monthly regimens are non-inferior to the 2.5 mg daily dose regimen.

Figure 4 Participants (%) considered responders to daily or once-monthly oral ibandronate (PP).

Figure 5 Time course of median (95% CI) change (%) from baseline in sCTX (PP).

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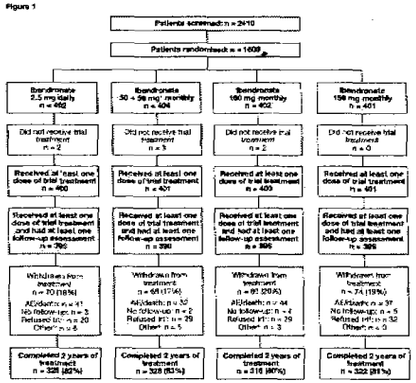
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Figure 1



*50 mg on two consecutive days

†Refused treatment includes 'did not cooperate' and 'withdrew consent'.

'Other' includes 'insufficient therapeutic response', 'early improvement', 'violation of selection criteria at entry' and 'other protocol violation'.

AE = adverse event.

trt = treatment.

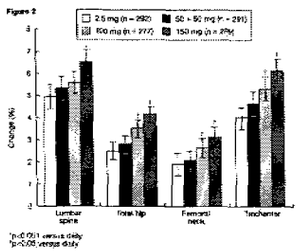
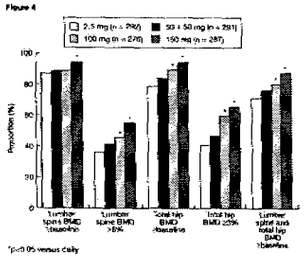

Figure 2
2.5 mg (n = 292)
50 + 50 mg (n = 291)
100 mg (n = 277)
150 mg (n = 284)
Change (%)
Lumbar spine
Total hip
Femoral neck
Trochanter
*p<0.05 versus daily
†p<0.05 versus daily

Figure 4



*p<0.05 versus daily

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Corrections

There was an error in table 1 of an article published in the May 2006 issue (Reginster J-Y, Adami S, Lakatos P, Greenwald M, Stepan JJ, Silverman SL. Efficacy and tolerability of once-monthly oral ibandronate in postmenopausal osteoporosis: 2 year results from the MOBILE study. *Ann Rheum Dis* 2006;**65**:654–661). In the header row of table 1 "50 + 5 mg monthly (n = 396)" should read "50 + 50 mg monthly (n = 396)".

Ann Rheum Dis 2008;**67**:280. doi:10.1136/ard.2005.044958.corr1

An error occurred in table 1 of a paper published in the May 2007 issue (de Jager W, Hoppenreijs PAH, Wulffraat NM, Wedderburn LR, Kuis W, Prakken BJ. Blood and synovial fluid cytokine signatures in patients with juvenile idiopathic arthritis: a cross-sectional study. *Ann Rheum Dis* 2007;**66**:589–98). The correct table is available online at http://ard.bmj.com/contents/vol67/issue2.

Ann Rheum Dis 2008;**67**:280. doi:10.1136/ard.2006.061853.corr1

Furst DE, Breedveld FC, Kalden JR, Smolen JS, Burmester GR, Sieper J, *et al*. Updated consensus statement on biological agents for the treatment of rheumatic diseases, 2007. *Ann Rheum Dis* 2007;**66**(Suppl III):iii2-22

This article mistakenly identifies all three anti-TNF agents (adalimumab, etanercept and infliximab) as having approval for the indication of juvenile idiopathic arthritis of the polyarticular type. Currently only etanercept holds this indication. The cited references to support the statement (refs 60-62) are all publications concerning etanercept.

Ann Rheum Dis 2008;**67**:280. doi:10.1136/ard.2007.081430.corr1

The authors of the article "Long-term follow-up results after autologous haematopoietic stem cell transplantation for severe systemic sclerosis" published in *Ann Rheum Dis* 2008;**67**:98–104 should have been listed in the following order: M C Vonk, Z Marjanovic, F H J van den Hoogen, S Zohar, A V M B Schattenberg, W E Fibbe, J Larghero, E Gluckman, F W M B Preijers, A P J van Dijk, J J Bax, P Roblot, P L C M van Riel, J M van Laar, D Farge. The error is regretted and a corrected version of the pdf will be published online: http://ard.bmj.com/cgi/content/full/ard.2007.071464/DC1

Ann Rheum Dis 2008;**67**:280. doi:10.1136/ard.2007.071464.corr1

Ibandronate Treatment for Osteoporosis: Rationale, Preclinical, and Clinical Development of Extended Dosing Regimens

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Ibandronate is a potent nitrogen-containing bisphosphonate available as a once-monthly oral formulation for the treatment and prevention of osteoporosis. Preclinical experiments with estrogen-depleted rats, dogs, and monkeys demonstrated the efficacy of daily and intermittent ibandronate dosing. Initial clinical trials explored the optimal dosing regimens for oral administration in humans. The Oral Ibandronate Osteoporosis Vertebral Fracture Trial in North America and Europe (BONE) and Monthly Oral Ibandronate in Ladies (MOBILE) trials demonstrated that long-term daily and intermittent administration of ibandronate was efficacious for increasing bone mineral density, reducing markers of bone turnover, and preventing fractures, while maintaining bone quality. These preclinical and clinical ibandronate trials provided progressive evidence that a simple, long interval dosing regimen could offer efficacy and safety comparable with currently available bisphosphonates. It is anticipated that once-monthly ibandronate may have a positive impact on patient adherence, and ultimately, on fracture protection in osteoporotic women.

Introduction

Bone mass is maintained as part of a balance between bone formation and resorption. In patients with postmenopausal osteoporosis (PMO), resorption exceeds formation, resulting in reduced bone mass and a deterioration of bone microarchitecture. Bisphosphonates, at clinically relevant doses, have been shown to reduce the rate of bone loss, increase bone mineral density (BMD), and reduce fracture risk [1].

The chemical structure of bisphosphonates is similar to that of inorganic pyrophosphate; however, bisphosphonates have a phosphorous-carbon-phosphorous backbone. Their high affinity for bone is due to a hydroxyl group at the R^1 position that binds to Ca^{2+} ions in hydroxyapatite bone mineral surfaces at sites of osteoclast activity [2]. The antiresorptive potency of individual bisphosphonates is determined by their R^2 side chain constituents [3].

Radio-labeled molecules were used to demonstrate that bisphosphonates are internalized by osteoclasts [4,5]. Once inside the osteoclasts, bisphosphonates containing nitrogen in the moiety at the R^2 position inhibit osteoclast function predominantly through inhibition of farnesyl pyrophosphate (FPP) synthase, an enzyme of the mevalonate pathway [2]. Inhibition of FPP synthase prevents prenylation of small GTPases such as members of the Ras, Rho, Rab, Rac, and Cdc42 subfamilies [2]. This, in turn, disrupts a variety of cell processes important for osteoclast function, including cytoskeletal rearrangement, membrane ruffling, and intracellular vesicle trafficking, resulting in osteoclast apoptosis [2,6]. Osteoclast apoptosis is not necessary for inhibition of bone resorption [7•]. Bisphosphonates also affect bone formation, mainly through reduction of activation frequency, as evidenced by a reduction in bone formation surfaces [8–10], but this occurs to a lesser extent than resorption [1]. The net result of bisphosphonate administration is a gain in BMD.

The duration of bisphosphonate action is dependent on a combination of factors, notably potency, dose, dosing interval, and bone turnover rate [11••]. It has been proposed that differences in the degree to which a bisphosphonate binds to bone are responsible for the varying persistence of its skeletal actions, affecting potency and duration of action [11••,12]. However, this may not be the case and the potency of inhibition of the FPP synthase system is considered to be a predominant

factor [2,13]. To facilitate intermittent dosing, a bisphosphonate must be biologically active in sufficient quantity to inhibit bone turnover for the entire between-dose interval and potent enough to maintain dosing within a range that is well tolerated but still effective [14].

Ibandronate is a highly potent, nitrogen-containing bisphosphonate. The tertiary nitrogen group in the R^2 side chain position, coupled with the hydroxyl group in its R^1 lateral chain, renders ibandronate approximately two-fold, 10-fold, 50-fold, and 500-fold more potent than risedronate, alendronate, pamidronate, and clodronate, respectively, as measured by bone resorption inhibitory activity in the arotinoid assay in rats [15]. As mentioned previously, potency is an important factor in the development of simplified dosing regimens with extended between-dose intervals. In this paper the preclinical evidence for extended dosing along with recently published clinical trial data in which the therapeutic advantages of ibandronate, hypothesized during the drug development process will be reviewed.

Preclinical Data

The World Health Organization has acknowledged the value of preclinical studies in the development of osteoporosis drugs [16]. Currently available bisphosphonates, notably alendronate, risedronate, and zoledronate, have been extensively tested in animal models [8,17–25]. In ovariectomized rats and nonhuman primates, these agents were shown to prevent bone turnover, while increasing BMD [8,17–21]. Studies in dogs have been used to examine micro-damage accumulation and have shown that long-term administration with pharmacologic doses of these compounds does not negatively affect bone quality [22–25].

Ibandronate efficacy has been demonstrated in four animal models, rat, dog, monkey, and mini-pig (not included in this review). Food and Drug Administration (FDA) guidelines recommend that agents for the prevention or treatment of osteoporosis be tested in two different species, the ovariectomized rat and a second non-rat model [26]. Ovariectomized rats are utilized because the bone loss observed in this animal model is similar to that experienced by postmenopausal women [27]. In both groups, there is an increase in bone turnover rate, with an initial phase of rapid bone loss followed-up by a period with a marked decrease, a higher degree of loss of cancellous versus cortical bone, and a decrease in calcium absorption [27]. Both rats and humans respond to treatment with estrogen therapy, tamoxifen, bisphosphonates, parathyroid hormone, calcitonin, vitamin D, and exercise [27]. The main difference between the two species is that rats do not undergo menopause during mid-life followed-up by a period of accelerated bone loss [27]. In addition, aged ovariectomized rats 8 months or older are a more appropriate model of PMO than younger, actively growing rats. By using older rats, ibandronate studies eliminated potential confounding factors, including bones that are still actively growing and age-dependent metabolic activities [28•].

In an initial dose-ranging study, 8-month old ovariectomized or sham-operated rats were treated immediately after surgery with daily ibandronate in doses from 0.1 to 30.0 μg/kg or vehicle. Ibandronate dose-dependently inhibited bone loss, as measured by changes in the radiographic density of the proximal metaphyses of the tibias [28•]. The optimal dose (the lowest dose that was not significantly different from the sham-operated solvent control) was 1 μg/kg/d [28•]. Administering a loading dose to attain an immediate steady-state level of drug, did not affect the results [28•].

In an extension of the study described above, varying treatment regimens were administered over a period of 20 to 22 weeks, such that the total cumulative dose per ovariectomized animal equaled 154 μg/kg [28•]. The between-treatment intervals were derived by taking into account the bone remodeling time in rats and findings that the effects of a single dose of ibandronate lasted 2 to 3 weeks in a model of retinoid-stimulated bone destruction [15]. The therapy-free intervals were chosen to be one, two, or three times the length of the bone turnover cycle in rats [28•]. Animals received 1 week "on" treatment, followed-up by a therapy-free interval of 2, 4, or 6 weeks [28•]. After completing the required number of cycles, the rats received an additional week "on" treatment. The radiographic densities of femurs from all groups of treated animals remained equivalent to those of sham-operated controls [28•]. This pivotal study demonstrated that the interval between doses could exceed estimated bone turnover time while maintaining efficacy.

In a follow-up study, 8-month old ovariectomized or sham-operated rats were treated, 10 weeks after surgery, with daily subcutaneous ibandronate (0.2 to 25 μg/kg) or intermittent ibandronate (25 or 125 μg/kg every 25 days) for 12 months [29]. The 10-week post-surgery interval allowed for substantial bone loss to accumulate prior to treatment. Concentrations of ibandronate in bone were linear with respect to dose, suggesting linear kinetics within the range administered. The skeletal uptake of ibandronate was related to total dose, regardless of administration schedule. Dose-dependent increases were seen in BMD, trabecular bone volume and trabecular number, load to failure, and yield loads in long bones and vertebrae [29].

As part of a long-term safety study, 6-week old female and male Wistar rats were given vehicle or 3, 7, or 15 mg/kg/d of ibandronate orally by gavage for 104 weeks. Compressive strength, BMD, and stiffness were significantly higher in ibandronate-treated versus vehicle-treated rats [30]. The doses of ibandronate given to the rats in this study far exceeded doses given in earlier studies to simulate long-term therapy. Lifelong administration of ibandronate increased BMD and maintained or improved bone quality [30].

Concerns have been discussed relating to long-term administration of bisphosphonates and the theoretic possibility the chronic reductions in bone turnover may result in accumulation of micro-fractures, normally repaired by bone remodeling, which could cause bone fatigue fractures [31]. Evidence supporting this concept was reported in a study involving long-term administration of etidronate in dogs [10]. In contrast, the ibandronate safety study in rats found significant increases in ultimate load and stress values with long-term ibandronate treatment [30]. The results indicate that micro-fracture accumulation and reduced compressive strength of vertebral bodies did not occur in the rat preclinical trials [30].

In addition to rats, dose-response osteoporosis prevention studies with ibandronate were performed in dogs. Ovariohysterectomized (OHX) dogs were injected subcutaneously with vehicle or ibandronate doses ranging from 0.1 to 100 μg/kg/d for 1 month [32]. The dogs given vehicle exhibited a significant decrease in bone volume within 1 month of OHX surgery [32]. Ibandronate, in doses of greater than or equal to 1 μg/kg/d, was required to prevent bone loss [32]. No adverse effects on bone structure, formation, or resorption were seen in sham-operated dogs receiving ibandronate at doses of 1 μg/kg/d [32].

In a second study that examined osteoporosis treatment in dogs, ibandronate was administered daily and intermittently for 1 year to OHX dogs 4 months after surgery (to allow for development of bone loss) [33]. Dogs on the intermittent ibandronate dosing regimen received the same cumulative dose as dogs receiving the highest continuous daily dose (3640 μg/kg/d) [33]. Dogs were monitored for 12 months after initiation of treatment. Ibandronate (14 μg/kg/d or intermittently dosed) completely reversed bone loss, as measured by bone volume, to levels similar to baseline values [33]. Intermittent dosing in this study did not significantly reduce or suppress bone turnover as determined by histomorphometry and bone mineral properties as measured by Fourier-transform infrared macrospectroscopy [33]. It was theorized that the 65 μg/kg/d intermittent dose would be sufficiently potent to suppress bone resorption while allowing more bone to form during the treatment-free periods [33].

In a study using a dog model developed to simulate fracture repair, 24-month old dogs received daily ibandronate, intermittent dosing of ibandronate with 2- to 6-week, dose-free intervals, or vehicle for 36 weeks [34]. Animals in the active dosing regimens all received the same total dose of ibandronate over the entire treatment period (252 μg/kg over 36 weeks) [34]. In week 27 or 28, tiny holes were drilled in the left tibia, and a bone marrow ablation was performed on the ipsilateral femur [34]. Ibandronate administration did not quantitatively or qualitatively affect the initial stage of bone repair healing and it did not affect the activation of cortical remodeling that occurs during the second stage of fracture healing [34].

Ibandronate was tested further in non-human primates, which are the most similar to humans as they have similar reproductive hormone patterns and menstrual cycles. Ovariectomized monkeys are considered the best model for studying the efficacy of anti-osteoporotic drugs [16]. After ovariectomies, cynomolgus monkeys exhibit changes in bone mass and turnover similar to what is observed in postmenopausal women [35,36].

In dose-ranging osteoporosis prevention studies in monkeys, 66 ovariectomized or sham-operated monkeys were given intravenous bolus injections of placebo or 10, 30, or 150 μg/kg of ibandronate at 30-day intervals for 16 months [16,37,38]. Doses were chosen based on the rat and dog studies and were meant to represent a suboptimal dose, the optimal effective dose, and five times the optimal dose [38]. Suboptimal dosing (10 μg/kg) of ibandronate only partially prevented OVX-induced effects [37]. Thirty μg/kg of ibandronate prevented osteopenia, while 150 μg/kg of ibandronate increased bone mass (measured by dual-energy x-ray absorptiometry [DXA] bone densitometry) and improved bone strength at the spine and femoral neck (measured by biomechanical testing of lumbar vertebrae—compression, whole ulnae in 3-point bending, and femoral neck strength), without having a negative effect on bone quality [37].

This was the first non-human primate study to use a bisphosphonate dosing schedule resembling a clinical regimen [11••,37]. Consequently, clinical trials with bolus intravenous administration of ibandronate every 3 months were initiated [39]. Data from monkeys were consistent with results obtained in phase II clinical trials [37–39]. Intravenous bolus injections of ibandronate every 3 months increased lumbar spine BMD by 5.2% after 12 months in postmenopausal women (2 mg) and approximately 4% in monkeys (eight monthly doses of 150 μg/kg/dose) [37,39].

Overall, the results from animal studies indicated that oral gavage, subcutaneous, or intravenous administration of ibandronate with extended dosing intervals reduced bone turnover, increased BMD, and maintained bone quality. Findings with all three species were consistent—ibandronate had a dose-dependent effect on BMD in estrogen-depleted animals. The optimal dose of ibandronate in rats, dogs, and monkeys was 1 μg/kg/d administered subcutaneously [28•,32,33,37].

Preclinical studies also demonstrated that bone quality was maintained with long-term administration of ibandronate, [30,33,34,37] a finding that is necessary for long-term safety. In rats receiving ibandronate for 104 weeks, bone quality was maintained or improved [30]. In both studies of OHX dogs receiving daily or intermittent ibandronate for 1 year and ovariectomized monkeys treated with monthly injections of ibandronate for 16 months, histomorphometric analyses demonstrated that bone structure remained normal [33,37]. The demonstrated efficacy of ibandronate for the prevention and

treatment of osteoporosis in animal models, coupled with maintenance of bone quality, provided the basis for the development of intermittent dosing regimens in clinical trials.

Phase I and II Studies

Phase I and II trials were aimed at determining the optimal dose and dosing frequency. Based on initial tests in rats comparing ibandronate with other bisphosphonates, the predicted active dose of ibandronate in humans was estimated to be approximately 0.8 to 1.0 mg/day [15].

The estimated range was expanded, and a placebo-controlled, dose-finding study was performed in which women received ibandronate in doses from 0.25 to 5.0 mg/d for 12 months [40]. Ibandronate 2.5 mg/d was determined to be the most effective dose (similar treatment effects were observed in patients receiving 5.0 mg/d) [40]. Oral daily ibandronate reduced bone turnover markers, increased total body bone mineral content, and significantly increased BMD at the lumbar spine, total proximal femur, trochanter, and femoral neck [40].

Similar results were seen in a separate study in which daily dosing was compared with intermittent dosing (2.5 mg of oral ibandronate daily or 20 mg oral ibandronate every other day for the first 24 days out of every 3 months) [41]. Significant reductions in bone markers of resorption and formation were observed and maintained throughout the study [41]. Daily and intermittent dosing led to similar numeric increases in BMD at the lumbar spine, total hip, trochanter, and femoral neck after 2 years [41].

A review of three ibandronate phase II studies noted that the efficacy achieved with ibandronate was similar regardless of treatment regimen, whether administered orally 2.5 mg daily, orally 20 mg every other day for 12 doses every 3 months, or intravenously once every 3 months [42]. There were comparable increases in BMD and significant reductions in biochemical markers of bone turnover with all three regimens tested [39–41].

Findings in phase I and II clinical trials served as the basis for the development of phase III studies such as the Oral Ibandronate Osteoporosis Vertebral Fracture Trial in North America and Europe (BONE) and the Monthly Oral Ibandronate in Ladies (MOBILE) trials, which evaluated daily and intermittent dosing ibandronate regimens in postmenopausal women.

BONE Study

The BONE trial was a 3-year, randomized, double-blind, placebo-controlled, parallel-group study, and the only ibandronate trial to date with a fracture endpoint. Postmenopausal women (n = 2946) with a BMD T-score of -2.0 to -5.0 in at least one vertebra (L1-L4) and one to four prevalent vertebral fractures (T4-L4) received placebo or oral ibandronate 2.5 mg daily or 20 mg every other day for 12 doses every 3 months [43•]. The primary endpoint of the study was the rate of new morphometric fractures with 3 years of treatment. Secondary measures included the rate of new or worsening vertebral fractures, clinical vertebral fractures, and clinical osteoporotic nonvertebral fractures, BMD changes at the lumbar spine and proximal femur, changes in levels of bone resorption and formation markers, and changes in height [43•].

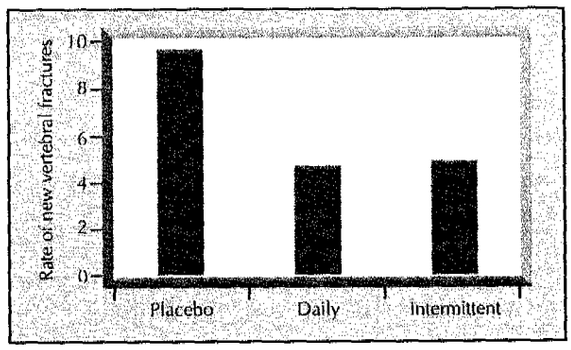


Figure 1. BONE study: incidence of new vertebral fractures after 3 years for patients dosed with daily and intermittent ibandronate and placebo.

Rate of new vertebral fractures was reduced in patients taking daily ibandronate (4.7%) and intermittent ibandronate (4.9%), compared with placebo (9.6%) (Fig. 1) [43•]. This corresponds to a reduction in the risk for new vertebral fractures of 52% (P = 0.0001) and 50% (P = 0.0006) for daily and intermittent dosing, respectively [43•]. Reductions in the incidence rates of new clinical vertebral fractures were 2.8% for daily and intermittent ibandronate dosing, compared with 5.3% for the placebo group [43•]; relative risk reduction of 49% for daily dosing, and 48% for intermittent dosing [43•]. In a post hoc analysis, it was determined that in higher-risk patients (baseline femoral neck BMD T-score of < -3.0), there was a reduction in the relative risk for nonvertebral fractures of 69% (P = 0.013) and 37% (P = 0.22) for daily and intermittent dosing, respectively. Significantly more height loss was observed in patients receiving placebo (5.6 mm) versus 3.9 mm (P = 0.0005) for daily and 4.7 mm (P = 0.0144) for intermittent dosing. Increases in lumbar spine BMD of 6.5%, 5.7%, and 1.3% were observed for daily, intermittent dosing, and placebo, respectively [43•]. Total hip BMD increased by 3.4% and 2.9% in the daily and intermittent dosing groups, respectively, while there was a net loss of 0.7% in the placebo group [43•]. Femoral neck BMD was increased by 2.8% and 2.4% in the daily and intermittent dosing groups, respectively, with a net loss of 0.6% in the placebo group [43•]. Trochanter BMD increased by 5.5%, 5.2%, and 0.2% in the daily, intermittent, and placebo groups, respectively [43•].

Within 3 months and throughout the 3-year study, there were significant reductions in bone resorption and

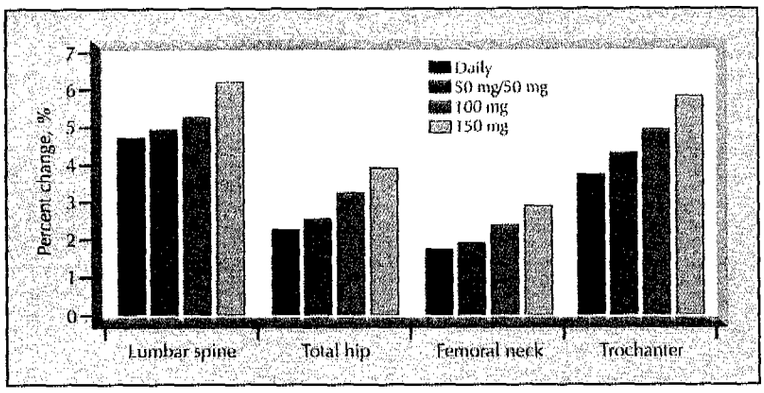


Figure 2. MOBILE study: changes from baseline in lumbar spine bone mineral density for patients treated with daily and intermittent ibandronate at 2 years.

formation markers in patients on both ibandronate treatment regimens versus placebo. C-telopeptide of type I collagen (CTX)/creatinine and N-telopeptide of type I collagen (NTX)/creatinine were reduced by 65.3% and 68.3% in the daily dosing group and 52.7% and 59.2% in the intermittent dosing group ($P < 0.001$ for both groups vs the placebo group) [44]. Levels of osteocalcin were reduced by 35.8% in the daily dosing group and 40.9% in the intermittent dosing group versus 2.1% in the placebo group ($P < 0.001$ for both ibandronate groups) [44].

A histomorphometric evaluation of a subgroup of patients from the BONE study assessed bone quality and architecture [45]. Patients underwent a transiliac bone biopsy at month 22 or 34 of treatment. In all cases, newly formed trabecular bone retained its structure with no indications of woven bone, marrow fibrosis, or signs of cellular toxicity [45]. A qualitative assessment found no impairment in bone matrix mineralization [45].

The BONE clinical trial demonstrated for the first time that significant fracture efficacy could be achieved with an intermittently administered bisphosphonate. While the study demonstrated that intermittent dosing was possible, the dosing regimen used in the study was not practical. The MOBILE study was initiated to examine efficacy with a more simplified dosing regimen (once monthly).

MOBILE Study

The MOBILE trial was a 2-year, randomized, double-blind, parallel-group, noninferiority, phase III ibandronate study and was the first bisphosphonate trial to evaluate a monthly oral regimen. Postmenopausal women ($n = 1609$) 55 to 80 years of age with osteoporosis (mean lumbar spine [L2-L4] BMD T-scores of -2.5 to -5.0) were included. Baseline assessments for the presence of vertebral fractures were not performed in this trial.

Upon enrollment, participants were randomized to one of four ibandronate treatment groups—2.5 mg daily, 50+50 mg once-monthly (50-mg dose given for 2 consecutive days), 100 mg once-monthly, and 150 mg once-monthly. Results from this study were analyzed after 1 and 2 years. The primary efficacy endpoint was the percent increase from baseline in lumbar spine BMD, as measured by DXA after 1 year. Secondary endpoints included measurements of BMD of the lumbar spine and proximal femur (total hip, femoral neck, trochanter) at 2 years. This information was used to assess the proportion of patients achieving predefined increases in the lumbar spine and total hip; measurements that have previously been identified as being associated with antifracture efficacy [46,47]. Changes from baseline in serum CTX (sCTX) concentrations were also measured at 3, 6, 12, and 24 months.

After 1 year, lumber spine BMD increased in the daily and monthly dosing groups [48•]. Noninferiority was established, given that the lower boundary of each one-sided 97.5% confidence interval was above the predetermined noninferiority margin for each comparison of a monthly versus the daily dose [48•]. Having demonstrated noninferiority, further testing was performed, which confirmed that the monthly dosing regimens and the 150-mg dose in particular, were superior to daily dosing [48•]. Lumbar spine BMD measurements increased in all treatment groups after 1 year. Numerically greater increases were seen in the once-monthly treatment groups compared with the daily dosing group. The largest increase was seen in patients receiving 150 mg of ibandronate monthly (4.9% vs 3.9% for daily dosing) [48•]. Increases in BMD were also seen in the proximal femur (total hip, femoral neck, trochanter) measurements, with the largest increases seen in the 150-mg dosing group [48•]. Decreases in sCTX were comparable in the daily and once-monthly dosing groups, 67.3% and 75.8% in the daily 2.5- and 150-mg monthly arms, respectively [48•].

Preliminary analyses of data after 2 years confirm the conclusions drawn from the first year's data—monthly ibandronate dosing is at least as effective as daily dosing for the treatment of osteoporosis [48•]. Increases in lumbar spine BMD were observed in the 150-mg once-monthly and daily treatment groups (6.6% and 5.0%, respectively) (Fig. 2) (Reginster, Unpublished data). This represented an increase in BMD from the first year results. Increases in proximal femur BMD (total hip, 4.2% and

2.5%; femoral neck, 3.1% and 1.9%; and trochanter, 6.2% and 4.0% for once-monthly and once-daily, respectively) were also observed. The decreases in sCTX, which were observed after 3 months, were maintained.

Conclusions

The development of extended dosing regimens for ibandronate was achieved through studies progressing from nonprimates, to nonhuman primates, to humans. Animal studies established that it was the cumulative dose of ibandronate, irrespective of dosing regimen, which was related to treatment effectiveness. These studies also demonstrated that bone quality was not compromised with long-term administration. The optimal subcutaneous dose of ibandronate, as determined in animal studies, was the equivalent of 1 μg/kg/d. Adjustments in dosing were made in human studies, which utilized oral administration, to account for the drug's low oral bio-availability.

Phase I and II studies determined the appropriate oral dosing levels and demonstrated the efficacy of ibandronate when administered using various intermittent dosing schedules in humans. Phase III trials, such as BONE and MOBILE, confirmed the long-term efficacy of ibandronate in humans with respect to multiple endpoints, including BMD, bone turnover markers, fracture rates, and bone quality. In the MOBILE study, the optimal dosage for once-monthly administration was determined. Ibandronate (150 mg) is currently the only bisphosphonate approved by the FDA for once-monthly oral dosing for the treatment and prevention of osteoporosis. Ibandronate is the first medication approved for monthly dosing of a chronic condition.

It remains a point of interest to determine the limits of the length of the between-dose interval. Since osteoclasts have a half-life of 2 to 3 weeks, this was believed to be the longest interval possible between bisphosphonate dosing. Studies with ibandronate have demonstrated that the dosing interval can be extended to once-monthly and beyond with maintenance of efficacy. It has been hypothesized that ibandronate released when the bone surface it is deposited on is resorbed may still be pharmacologically active. The limits of the administered doses and between-dose intervals have yet to be determined.

Results from a crossover trial evaluating patient preferences for once-weekly alendronate versus once-monthly ibandronate demonstrated that the majority of patients prefer the once-monthly regimen because it is "easier to follow for a long time" (Emkey, Unpublished data). Given that approximately 50% of patients treated for osteoporosis remain adherent to therapy at 1 year [49,50], strategies must be advanced to support better adherence for women with osteoporosis. While many factors impact adherence to bisphosphonates such as dosing frequency, difficult to tolerate side effects, and complexity of the treatment protocol, it is likely that the reduced medication burden offered by a once-monthly formulation can have a positive impact.

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- •• Of major importance

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

Radicación No. 04-096462
Clasificación Internacional (IPC): A61K31/663
Concepto Técnico No. 02156

Patente de Invención	■	Patente de Modelo de Utilidad		☐	
Vía Nacional	☐				
Vía PCT (fase nacional)	■	Cap.I	☐	Cap. II	■

No. Sol. Internacional PCT/EP03/04629
Fecha de Presentación Internal. 02 de Mayo de 2003

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

Descripción: Folios: 61 a 103 como se radicó inicialmente
Reivindicaciones: Folios 18 a 20 como se radicó inicialmente
Folios 51 a 52 modificadas en fase nacional
Folios 109 a 110 modificadas en fase nacional
Folios 170 modificadas en fase nacional
Prioridad: Folios: 1 -f 206
10 de Mayo de 2002, EP, 02010136.6

Respuesta del solicitante: Folios: 93 a 123, 141 a 169, 171 a 190

2. Objeto de la invención

- Título de la solicitud: **"ÁCIDO BIFOSFÓNICO PARA EL TRATAMIENTO Y PREVENCIÓN DE OSTEOPOROSIS"** Folio 1.

El objeto de la presente solicitud de patente de invención consiste en el empleo de los ácidos bifosfónicos o las sales farmacéuticamente aceptables de los mismos, especialmente el ácido ibandrónico para la prevención y tratamiento de la osteoporosis.

El problema planteado en esta solicitud es la prevención o tratamiento de trastornos caracterizados por un aumento patológico de la resorción ósea.
Para solucionar este problema técnico la solicitud en estudio proporciona un medicamento de un ácido bifosfónicos o las sales farmacéuticamente aceptables de los mismos.

- **Clasificación Internacional de Patentes (IPC):** *A61K31/663*

3. Determinación del Estado de la Técnica

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es: 13/11/2000 se encontraron los siguientes documentos del estado de la técnica relacionados, que pueden afectar la

patentabilidad del objeto de la presente solicitud:

N°	Documento	Título	Fecha de publicación
D1	US 6,143,326	"Oral pharmaceutical preparation containing ibandronat"	30/10/1997
D2	WO 00/21541	"Process for the preparation of oral pharmaceutical compositions comprising biphosphonates"	20/04/2000

7. Análisis de patentabilidad (artículo 14 D486)

Nivel inventivo (artículo18 D486)

La reivindicación 1 se refiere a un medicamento para administración oral caracterizado porque es un comprimido recubierto por una película en donde el núcleo comprimido comprende:

- 150mg de ácido ibándrónico o una sal farmacéuticamente aceptable del mismo y
- Uno o más excipientes farmacéuticamente aceptables seleccionados del grupo conformado por: lactosa, polivinilpirrolidona, celulosa microcristalina, crospovidona, ácido esteárico y dióxido de silicio

y en donde el recubrimiento del comprimido comprende uno o más excipientes farmacéuticamente aceptables seleccionados entre el grupo conformado por: hidroxipropil metilcelulosa, dióxido de titanio, talco y polietilénglicol 6000

Recubierta

D1 divulga una formulación que comprende un núcleo de tableta que contiene entre **0.1 a 100mg de ibandronato** y una cubierta la cual es libre de ibandronato con la siguiente proporción: (Ver columna 6, líneas 46-56)

- **51.425%** por peso de **hidroxipropilmetilcelulosa**
- **24.650%** por peso de **dióxido de titanio**
- **15.000%** por peso de **polietilénglicol**
- **8.925%** por peso de **talco**

El ejemplo de la solicitud presentada utiliza en las tabletas de 50mg de ibandronato los mismos excipientes enunciados en **D1** para la película de recubrimiento donde se utilizan como excipientes: hidroxipropilmetilcelulosa, óxido de titanio, talco y Polietilénglicol por considerarse contenida, superpuesta y sugerida en la película de **D1** (Ver folio 169):

Tabla 1 "Película"

Solicitud presentada-Recubrimiento	**D1**
Hidroxipropilmetilcelulosa	SI (Ver columna 6, línea 51)
Dióxido de Titanio	SI (Ver columna 6, línea 52)
Talco	SI (Ver columna 6, línea 54)
Polietilénglicol 6000	SI (Ver columna 6, línea 53)

Núcleos:

D2 divulga previamente un proceso para la preparación de composiciones farmacéuticas orales que comprenden bifosfonatos. (Ver resumen)

El ibandronato es la sustancia activa preferida en **D2** particularmente en la forma de monohidrato de ibandronato sódico en una proporción hasta 50mg. (Ver página 6, líneas 1-7)

El ejemplo 3 y 4 de **D2**, enseñan formulaciones para tabletas las cuales contienen lactosa, polivinilpirrolidona, celulosa microcristalina, crospovidona, ácido esteárico y dióxido de silicio (Ver página 10 y 11).

La reivindicación 7 enseña que los adyuvantes usados se encuentran en las proporciones de lactosa en 1-99% por peso, polivinilpirrolidona en 0.1-20% por peso, celulosa microcristalina en 1-99% por peso. (Ver página 14, líneas 8-11-D2)

La reivindicación 9 enseña que el proceso aplica a tabletas recubiertas. (Ver página 14, líneas 19-20-**D2**)

La reivindicación 10 se refiere al peso de ácido esteárico a la mezcla en una proporción de 0.05-3% (Ver página 14, líneas 24-26-**D2**)

El solicitante en el ejemplo enseña los mismos componentes previamente divulgados para el núcleo de las tabletas tales como lactosa en 1-99% por peso, polivinilpirrolidona en 0.1-20% por peso, celulosa microcristalina en 1-99% por peso, crospovidona y dióxido de silicio (Ver folio 50).

Tabla 1 "Núcleos"

Solicitud presentada Núcleos	**D2** (Ejemplo 3-Página 10)
Lactosa	SI
Polivinilpirrolidona	SI
Celulosa Microcristalina	SI (Ver columna 6, línea 54)
Crospovidona	SI
Ácido esteárico	SI
Dióxido de Silicio	SI

La diferencia de la solicitud presentada con **D1** y **D2** es la concentración del fármaco, la cual es de 150mg, en las anterioridades las dosis son más bajas.

Es evidente para el experto en la materia que de acuerdo a lo previamente divulgado en **D1** y **D2,** se obtendría el medicamento oral de ibandronato monosódico monohidrato en comprimidos recubiertos de 150mg, empleando los mismos excipientes antes enseñados previamente tales como lactosa, polivinilpirrolidona, celulosa microcristalina, crospovidona, ácido esteárico y dióxido de silicio e hidroxipropilmetilcelulosa en los núcleos, y óxido de titanio, talco y polietilénglicol en la recubierta, aumentando la cantidad de fármaco en la composición, sin la necesidad de emplear habilidad inventiva.

De acuerdo con lo anterior la solicitud resulta obvia pues se parte de un núcleo y una cubierta ya conocidos en el estado de la técnica para el ácido ibandrónico o sus sales. Ya existían concentraciones hasta 100mg del fármaco y el solicitante sólo emplea 150mg.Esta modificación en la concentración, puede ser realizada fácilmente

por una persona medianamente versada en el arte de acuerdo con sus conocimientos en farmacología, en cuanto a las dosis y concentraciones permitidas en humanos. La solicitud se deriva de forma evidente del estado de la técnica, por lo tanto carece de nivel inventivo.

El problema técnico planteado en esta solicitud como es obtener **"es la prevención o tratamiento de trastornos caracterizados por un aumento patológico de la resorción ósea",** sería solucionado fácilmente por el experto en la materia con base en las composiciones farmacéuticas divulgadas en **D1** y **D2**, de manera que este lo lograría fácil y obviamente sin necesidad de emplear Habilidad Inventiva.

8. Respuesta a los argumentos del solicitante:

- El solicitante en Folios 202 realiza el análisis técnico de la solicitud basado en la actividad farmacológica, el cual es el resultado a alcanzar de la solicitud presentada, es decir sus eventuales ventajas técnicas en un método de tratamiento. Es obvio que al aumentar la concentración del fármaco a 150mg se aumente su potencia; de acuerdo con el comportamiento clínico referido como el resultado de un descubrimiento terapéutico (Ver Folios 38, linea 28 y página 39, líneas 1-7), y obtener mejores resultados con la composición. Por lo tanto no se evidencia la utilización de altura inventiva en la solicitud.
- El solicitante se refiere en el Folio 203b: *por qué una persona sugeriría una composición que comprende 150mg de ácido ibandrónico, es decir una composición que comprende el 200% de la dosis conocida en el arte previo para tratar los efectos de la resorción ósea?* Estas sugerencias surgen derivadas del uso del fármaco en terapia, como se expresa a lo largo del capítulo descriptivo (Ver Solicitud-Folios 37, líneas 26-28, Folios). Esta modificación no aporta ni supera la tecnología farmacéutica anterior de composiciones de ibandronato, sólo mejora el uso o empleo del fármaco en un método de tratamiento por el aumento de la dosis.
- El solicitante modifica el objeto de la invención del empleo de los ácidos bifosfónicos a medicamento. El capítulo descriptivo en general se refiere al método de administración del medicamento.

9. Conclusión:

En consecuencia y por todo lo expuesto anteriormente, se recomienda **Negar** las reivindicaciones: 1-2 (Folios: 206)

Bogotá, D.C.,

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