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Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E.

S.

D.

REF: EXPEDIENTE 04-096-462

TÍTULO SOLICITADO: "Ácido bifosfónico para el tratamiento y prevención de la osteoporosis"

PUBLICACIÓN: Gaceta 547 de 30-12-2004, número de publicación 685

PRIORIDAD : EP 02010136,6 de mayo 10 de 2002

SOLICITANTE: F. HOFFMANN-LA ROCHE AG

APODERADO: ALICIA LLOREDA RICAURTE

TRÁMITE: REMISIÓN DE INFORMACIÓN

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **TECNOQUÍMICAS S.A.**, con el propósito de coadyuvar en la decisión que sobre la solicitud de patente de la referencia habrá de adoptarse próximamente, me permito remitir información fundamentada para demostrar que la misma incumple los requisitos materiales de patentabilidad establecidos por la Decisión 486 de 2000 de la Comunidad Andina de Naciones, y que por ello no es merecedora del privilegio de patente solicitado.

En tanto la materia revelada en esta solicitud carece por completo de novedad y nivel inventivo, su eventual concesión no sólo supondría la violación directa de la

normativa vigente en materia de patentes, sino que constituiría una barrera inaceptable para la libre competencia.

PETICIÓN

Sírvase negar el beneficio patentario a la solicitud contenida en el expediente 04-096-462, debido al evidente incumplimiento de los requisitos de patentabilidad a que se refieren los artículos 14, 16 y 18 de la Decisión 486 de la Comunidad Andina de Naciones, con base en los fundamentos que se expondrán en este escrito.

II. FUNDAMENTOS DE LA PETICIÓN

2.1. El empleo de un ácido bifosfónico o la sal farmacéuticamente aceptable del mismo para la elaboración de un medicamento para la prevención o tratamiento de trastornos caracterizados por un aumento patológico de la resorción ósea, revelados en la solicitud **04-096-462**, carecen de novedad y nivel inventivo por obra de las revelaciones previas comprendidas en las siguientes anterioridades:

- La solicitud internacional PCT WO 01/15703 A1 "METHOD FOR INHIBITING BONE RESORPTION" publicada el **8 de marzo de 2001**, revela métodos para inhibir la resorción ósea en animales, los cuales minimizan la ocurrencia de potenciales efectos gastrointestinales adversos. De igual manera, el documento en cuestión revela composiciones farmacéuticas y kits para prevenir dicha resorción ósea.

Más específicamente, la solicitud mencionada revela un método de tratamiento de la resorción ósea que comprende la administración oral de una cantidad farmacéuticamente efectiva de un bifosfonato seleccionado del grupo que consiste de alendronato, ibandronato, risedronato, sales o ésteres farmacéuticamente aceptables del mismo, como unidades de dosificación, de acuerdo con un programa continuo que tiene un intervalo de medicación seleccionado del grupo que consiste de dosificación una vez a la semana, dos veces a la semana, cada dos semanas, y medicación dos veces al mes.

En necesario concluir que la materia revelada afecta la Novedad y el Nivel Inventivo de la solicitud en curso, particularmente respecto de las reivindicaciones 1, 4, 9 y 10, tal como se explica a continuación:

- La reivindicación 1 revela el empleo de un ácido bifosfónico o una sal del mismo en la elaboración de un medicamento útil en el tratamiento de trastornos óseos, que puede ser administrado oralmente en uno, dos o tres días consecutivos al mes;
- La reivindicación 4 describe que el ácido bifosfónico es el ácido ibandrónico o una sal farmacéuticamente aceptable del mismo;
- Las reivindicaciones 9 y 10 revelan que el medicamento se administra en forma de dosis única o en forma de subdosis múltiples.

Del mismo modo, las reivindicaciones 1, 4 y 7 a 10 de la solicitud internacional PCT/WO01/15703 mencionada anticipan la materia revelada en las reivindicaciones 1 y 3 a 7 de la solicitud colombiana en trámite, en tanto la publicación internacional revela un método para la inhibición de la resorción ósea en donde el bifosfonato se encuentra en una cantidad entre 3.5mg y 200mg, el cual puede ser seleccionado del grupo de Ibandronato, sus sales o ésteres farmacéuticamente aceptable o mezclas del mismo, y la solicitud en trámite describe que la dosis eficaz del ácido bifosfónico está entre 100mg y 150mg el cual corresponde al ácido ibandrónico o una sal aceptable del mismo, como es la sal sódica del ácido ibandrónico monohidrato.

- Por su parte, el artículo "Ibandronate: A Comparison of oral daily doping versus intermittent doping in postmenopausal osteoporosis"; B.J. Riis; J. Ise; T. Von Stein, Y. Bagger and C. Christiansen, publicado en Journal of Bone and mineral research, Vol 16, Number 10, 2001, revela:

ABSTRACT

The objective of this study was to compare efficacy and safety of continuous versus intermittent oral dosing of ibandronate. Two hundred forty women aged 55–75 years with postmenopausal osteoporosis were randomized to active treatment or placebo. Similar total doses of ibandronate were provided by treatment regimens with either continuous 2.5 mg of ibandronate daily ($n = 51$) or intermittent 20 mg of ibandronate every other day for the first 24 days, followed by 9 weeks without active drug ($n = 51$). The placebo group (total $n = 51$) was crossed over after 12 months to receive either continuous ($n = 31$) or intermittent ibandronate ($n = 35$). By 24 months, bone mineral density (BMD) had increased significantly relative to baseline in both active treatment groups. The continuous and intermittent groups showed statistically equivalent increases in lumbar spine BMD of $+5.64\%$ (± 0.53) and $+5.54\%$ (± 0.53) and in total hip of $+3.35\%$ (± 0.40) and $+3.41\%$ (± 0.40), respectively (per protocol population). Biochemical markers of bone turnover decreased significantly in both treatment groups. The level of marker suppression was similar, although the intermittent group displayed, as expected, more fluctuation over the treatment period. The frequency of adverse events was similar in the treatment groups. In conclusion, the intermittent and continuous regimens showed equivalent changes in BMD and bone turnover. These results confirm previous preclinical findings indicating that the efficacy of ibandronate depends on the total oral dose given rather than on the dosing schedule. This supports development of new flexible dosing regimens targeted to minimize the frequency of dosing, which are expected to improve convenience and lead to enhanced long-term patient compliance. (J Bone Miner Res 2001;16:1871–1878)

La publicación transcrita no solo demuestra el conocimiento previo del empleo de un ácido bifosfónico como Ibandronato para el tratamiento de trastornos de la resorción ósea, sino el mismo régimen propuesto en la reivindicación 1 de la solicitud colombiana en trámite. Es por ello que la administración del medicamento oralmente en uno, dos o tres días consecutivos al mes carece de novedad, pues ya en el año 2001 ya se había revelado la posibilidad de hacer dicha administración de Ibandronato para el tratamiento de la Osteoporosis en forma continua (dosis diaria oral) o en forma intermitente (cada dos días), por 24 días, seguido por un término de 9 semanas sin principio activo.

- De igual manera, la solicitud internacional PCT WO97/39755A1 "ORAL PHARMACEUTICAL PREPARATION CONTAINING IBANDRONAT" publicada el 30 de octubre de 1997, y equivalente a la patente americana US 6,143,326 publicada el 7 de noviembre de 2000, revela formulaciones farmacéuticas para aplicación oral que contienen Ibandronato o una sal farmacéuticamente aceptable del mismo, y procesos para producir las mismas.

Las formulaciones orales sólidas de Ibandronato allí reveladas constan de un núcleo que contiene la sustancia activa, la cual es cubierta con un adyuvante de cubierta libre de sustancia activa, la cual se disuelve independientemente del pH o es removida de la formulación oral al contacto con el jugo digestivo. Los ejemplos de la solicitud internacional en mención, describen formulaciones donde el Ibandronato es empleado como sustancia activa en cantidades entre

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0.1 y 100mg por unidad de dosis y que además posee una película de recubrimiento, veamos:

EXAMPLE 1

Tablets containing 0.1g			
Tablet area [mg] in 200 mg tablet area	10.0	20.0	80.0
Tablet area [mg]			
Methylhydroxypropylcellulose	5.1425	5.1425	5.1425
Titanium dioxide	2.4650	2.4650	2.4650
Macrogol	1.5000	1.5000	1.5000
Talc	0.8905	0.8905	0.8905
Total amount	10.0000	10.0000	10.0000

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

EXAMPLE 3

Tablets containing 0.1g			
Tablet area [mg] in 200 mg tablet area	10.0	20.0	80.0
Tablet area [mg]			
Talc	2.00	2.00	2.00
Macrogol	1.50	1.50	1.50
Methylhydroxypropylcellulose	0.80	0.80	0.80
Titanium dioxide	0.80	0.80	0.80
Macrogol	0.20	0.20	0.20
Ethylmethylmethacrylate copolymer	0.05	0.15	0.15
Stearate	0.05	0.05	0.05
Total amount	5.40	5.40	5.40

Polysorbate 80 in the form of Polysorbate 80 NF 510 as an aqueous dispersion.

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

Es necesario concluir que el documento citado describe las mismas características generales de la composición reclamada en la solicitud en trámite, especialmente lo revelado en la reivindicación 9 es decir, un ácido bifosfónico o una sal del mismo como es lbandronato, comprimido recubierto por una película, y excipientes adecuados, bien sea lubricantes, de relleno, enlazantes, desintegrantes, entre otros —algunos de ellos comunes para ambos documentos, por ejemplo, hidroxipropilmetilcelulosa, dióxido de titanio, talco y polietilenglicol 6000-. La comprensión general de todas las características de la composición ahora reclamada en documentos publicados con bastante antelación a la fecha de prioridad

(2002) demuestra que la solicitud colombiana 04-096-462 carece por completo de Nivel Inventivo, y aún de Novedad, pues una persona medianamente versada en el arte respectivo, conociendo el contenido de la citada anterioridad y combinándolo con enseñanzas generales disponibles en materia de formulación farmacéutica, necesariamente derivaría en forma evidente el objeto que ahora se reivindica.

Vale reiterar aquí que la materia reivindicada se refiere a una forma de presentación farmacéutica convencional de un principio activo igualmente conocido, pretensión que incumple el requisito de Nivel Inventivo que debería acreditar para hacerse merecedora al privilegio de patente que solicita.

- Ahora bien, en este punto vale anotar que la presente solicitud involucra en la memoria descriptiva y reivindicaciones el USO de un ácido bifosfónico ó una sal farmacéuticamente aceptable para la manufactura de un medicamento para la prevención o tratamiento de desordenes caracterizados por el patológico incremento de la resorción del hueso e involucra una especificación de DOSIS diaria en un tiempo de dos a tres días por mes, al paso que la reivindicación 7 describe que el ácido bifosfónico corresponde al ácido Ibandrónico, sal monosódica forma monohidrato.

Al respecto basta anotar que la definición de dosis y concentraciones es parte esencial de la terapéutica, tal como se ha explicado en diversas publicaciones conocidas per se, entre ellas Goodman & Gilman¹, en donde se ha explicado que *"Dado que todos los enfermos difieren en sus reacciones o respuestas a los fármacos, cada 'encuentro' terapéutico debe ser considerado como un experimento en el que se somete a prueba una hipótesis. El fundamento científico de dicha hipótesis proviene de la base de datos generada en estudios con testigos en seres humanos durante las diversas fases de obtención y estudios del agente, y la experiencia obtenida después de su distribución comercial."*

¹ Goodman & Gilman. A. G., Las bases farmacológicas de la terapéutica. 9na Ed. Interamericana. 1996. México Pág. 47

Más adelante la misma publicación explica que *"La individualización del tratamiento en un paciente particular exige conocimientos básicos de farmacocinética y farmacodinámica. Son innumerables los factores que influyen en la reacción de un sujeto a un fármaco; por ejemplo, su edad, la enfermedad de órganos por los que se elimina el medicamento (riñones o hígado), el empleo concomitante de otros productos farmacéuticos, alimentos y sustancias químicas (interacciones medicamentosas); la administración previa del mismo fármaco u otros semejantes (tolerancia), y diversos factores genéticos que influyen en la cinética y toxicidad de los medicamentos (farmacogenética)"*.

La referencia anterior permite concluir que en tanto la dosificación en función de la concentración y tiempo de administración son parte fundamental de la individualización del tratamiento, lo que pretende el solicitante es obtener privilegio de patente sobre un método de terapéutico.

Ahora bien, en lo referente a la forma de presentación de monohidrato de una de las sales de una molécula existente en el estado de la técnica, como es el ácido ibandronico, es del caso recordar que nada tiene de novedoso o inventivo el hecho de que un principio activo se encuentre en forma monohidratada, pues resulta evidente que la hidratación o la deshidratación de moléculas son métodos ampliamente conocidos y empleados en la industria química.

En el mismo sentido hago notar que los hidratos son una forma de presentarse las sustancias cuando éstas cristalizan en el disolvente universal —el agua— y retienen moléculas del disolvente en la red de cristalización; es por ello que se consideran aplicables al caso en estudio algunos argumentos relacionados con la carencia de nivel inventivo envuelta en la caracterización de sustancias químicas en función de su forma de presentación polimórfica.

Por lo expuesto respetuosamente llamo la atención sobre el hecho de que la solicitud de la referencia, en todas sus reivindicaciones, no cumple con los requisitos dispuestos en la Decisión 486 de 2000, por tal razón no puede ser objeto de privilegio de patente de invención.

III. PRUEBAS

Ruego que se tengan como tales, sin perjuicio de que el Despacho considere oficiosamente, las siguientes:

- PCT WO 01/15703 A1 "METHOD FOR INHIBITING BONE RESORPTION" de marzo 8 de 2001, página 12 y capítulo reivindicatorio.
- Artículo "Ibandronate: A Comparison of oral daily doping versus intermittent doping in postmenopausal osteoporosis"; B.J. Riis; J. Ise; T. Von Stein, Y. Bagger and C. Christiansen, publicado en Journal of Bone and mineral research, Vol 16, Number 10, 2001.
- Primera página y columnas 5 y 6 de la patente US 6,143,326 de noviembre 7 de 2000.

Señor Superintendente,



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T.P.A 44.655 del C.S.J.

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US 09/388,659 (CIP)
Filed on 2 September 1999 (02.09.1999)

(71) Applicant (for all designated States except US): MERCK & CO., INC. [US/US]; 126 East Lincoln Avenue, Rahway, NJ 07065-0907 (US).

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(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) Title: METHOD FOR INHIBITING BONE RESORPTION



(57) Abstract: Disclosed are methods for inhibiting bone resorption in mammals while minimizing the occurrence of or potential for adverse gastrointestinal effects. Also disclosed are pharmaceutical compositions and kits for carrying out the therapeutic methods disclosed herein.

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of a unit dosage of the bisphosphonate every other Sunday. It is preferred that the unit dosage is not administered on consecutive days, but the biweekly dosing regimen can include a dosing regimen in which the unit dosage is administered on two consecutive days within two different biweekly periods.

5 By twice-monthly dosing is meant that a unit dosage of the bisphosphonate is administered twice, i.e. two times, during a monthly calendar period. With the twice-monthly regimen, the doses are preferably given on the same two dates of each month. In the twice-monthly dosing regimen, each unit dosage is generally administered about every fourteen to sixteen days. A nonlimiting example
10 of a biweekly dosing regimen would entail dosing on or about the first of the month and on or about the fifteenth, i.e. the midway point, of the month. It is preferred that the unit dosages are not administered on the same or consecutive days but the twice-monthly dosing regimen can include a dosing regimen in which the unit dosages are administered on two consecutive days within a monthly period, or different monthly
15 periods. The twice-monthly regimen is defined herein as being distinct from, and not encompassing, the biweekly dosing regimen because the two regimens have a different periodicity and result in the administration of different numbers of dosages over long periods of time. For example, over a one year period, a total of about twenty four dosages would be administered according to the twice-monthly regimen
20 (because there are twelve calendar months in a year), whereas a total of about twenty six dosages would be administered according to the biweekly dosing regimen (because there are about fifty-two weeks in a year).

In further embodiments or descriptions of the present invention, the unit dosage is given with a periodicity ranging from about once every 3 days to about
25 once every 16 days.

The methods and compositions of the present invention are useful for inhibiting bone resorption and for treating and preventing abnormal bone resorption and conditions associated therewith. Such conditions include both generalized and localized bone loss. Also, the creation of bone having an abnormal structure, as in
30 Paget's disease, can be associated with abnormal bone resorption. The term "generalized bone loss" means bone loss at multiple skeletal sites or throughout the skeletal system. The term "localized bone loss" means bone loss at one or more specific, defined skeletal sites.

Generalized bone loss is often associated with osteoporosis.
35 Osteoporosis is most common in post-menopausal women, wherein estrogen

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WHAT IS CLAIMED IS:

1. A method for inhibiting bone resorption in a mammal, said method comprising orally administering to said mammal a pharmaceutically effective amount
5 of a bisphosphonate selected from the group consisting of alendronate, ibandronate, risedronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof as a unit dosage according to a continuous schedule having a dosing interval selected from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.
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2. A method according to Claim 1 wherein said mammal is a human.
3. A method according to Claim 2 wherein said dosing interval is
15 once-weekly.
4. A method according to Claim 3 wherein said unit dosage of said bisphosphonate comprises from about 3.5 mg to about 200 mg, on an acid active basis, of a bisphosphonate selected from the group consisting of ibandronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.
20
5. A method according to Claim 3 wherein said unit dosage of said bisphosphonate comprises from about 3.5 mg to about 200 mg, on an acid active basis, of a bisphosphonate selected from the group consisting of risedronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.
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6. A method according to Claim 5 wherein said pharmaceutically acceptable salt is risedronate monosodium hemi-pentahydrate.
7. A pharmaceutical composition comprising about 35 mg, on an
30 acid active basis, of a bisphosphonate selected from the group consisting of ibandronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.
8. A pharmaceutical composition comprising about 40 mg, on an
35 acid active basis, of a bisphosphonate selected from the group consisting of ibandronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.

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- 5 9. A pharmaceutical composition comprising about 45 mg, on an acid active basis, of a bisphosphonate selected from the group consisting of ibandronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.
- 10 10. A pharmaceutical composition comprising about 50 mg, on an acid active basis, of a bisphosphonate selected from the group consisting of ibandronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.
- 15 11. A pharmaceutical composition comprising about 35 mg, on an acid active basis, of a bisphosphonate selected from the group consisting of risedronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.
- 20 12. A pharmaceutical composition comprising about 40 mg, on an acid active basis, of a bisphosphonate selected from the group consisting of risedronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.
- 25 13. A pharmaceutical composition comprising about 45 mg, on an acid active basis, of a bisphosphonate selected from the group consisting of risedronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.
- 30 14. A pharmaceutical composition comprising about 50 mg, on an acid active basis, of a bisphosphonate selected from the group consisting of risedronate, pharmaceutically acceptable salts or esters thereof, and mixtures thereof.
15. A pharmaceutical composition according to any of claims 11-14 wherein said pharmaceutically acceptable salt is risedronate monosodium hemipentahydrate
16. A kit for inhibiting bone resorption in a mammal, said kit comprising at least one pharmaceutically effective unit dosage of a bisphosphonate selected from the group consisting of alendronate, ibandronate, risedronate, pharmaceutically acceptable salts or ester thereof, and mixtures thereof, for oral administration according to a continuous schedule having a dosing interval selected

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from the group consisting of once-weekly dosing, twice-weekly dosing, biweekly dosing, and twice-monthly dosing.

Ibandronate: A Comparison of Oral Daily Dosing Versus Intermittent Dosing in Postmenopausal Osteoporosis

B.J. RIIS,^{1,2} J. ISE,^{3,4} T. VON STEIN,^{3,5} Y. BAGGER,¹ and C. CHRISTIANSEN^{1,6}

ABSTRACT

The objective of this study was to compare efficacy and safety of continuous versus intermittent oral dosing of ibandronate. Two hundred forty women aged 55–75 years with postmenopausal osteoporosis were randomized to active treatment or placebo. Similar total doses of ibandronate were provided by treatment regimens with either continuous 2.5 mg of ibandronate daily ($n = 81$) or intermittent 20 mg of ibandronate every other day for the first 24 days, followed by 9 weeks without active drug ($n = 78$). The placebo group (total, $n = 81$) was crossed over after 12 months to receive either continuous ($n = 37$) or intermittent ibandronate ($n = 35$). By 24 months, bone mineral density (BMD) had increased significantly relative to baseline in both active treatment groups. The continuous and intermittent groups showed statistically equivalent increases in lumbar spine BMD of +5.64% (± 0.53) and +5.54% (± 0.53) and in total hip of +3.35% (± 0.40) and +3.41% (± 0.40), respectively (per protocol population). Biochemical markers of bone turnover decreased significantly in both treatment groups. The level of marker suppression was similar, although the intermittent group displayed, as expected, more fluctuation over the treatment period. The frequency of adverse events was similar in the treatment groups. In conclusion, the intermittent and continuous regimens showed equivalent changes in BMD and bone turnover. These results confirm previous preclinical findings indicating that the efficacy of ibandronate depends on the total oral dose given rather than on the dosing schedule. This supports development of new flexible dosing regimens targeted to minimize the frequency of dosing, which are expected to improve convenience and lead to enhanced long-term patient compliance. (*J Bone Miner Res* 2001;16:1871–1878)

Key words: ibandronate, intermittent dosing, osteoporosis, bone mineral density, bone markers

INTRODUCTION

BISPHOSPHONATES ARE highly potent inhibitors of osteoclast-mediated bone resorption both in vitro and in vivo. The nitrogen-containing bisphosphonates inhibit bone

resorption by various mechanisms including the acceleration of osteoclast apoptosis via inhibition of the mevalonic acid pathway and protein prenylation.⁽¹⁾ Etidronate, alendronate, and recently risedronate have been approved for the treatment and prevention of osteoporosis (etidronate was

¹Center for Clinical and Basic Research, Ballerup, Denmark.

²Bonni Riis is a research physician at the Center for Clinical and Basic Research and served as an ad hoc consultant for Beigis Escu-Vesco, Boehringer Mannheim, Chiesi, Croupe Fournier Roche, Eli Lilly, MSD, Novo Nordisk, Pfizer, Procter and Gamble, Sandoz (now Novartis), and Wyeth-Ayerst. Dr. Riis also is the founder of Osteometer Biotech A/S.

³Roche Global Development, Mannheim, Germany, and Palo Alto, California, USA

⁴Jürgen Ise is an employee of Roche Diagnostics.

⁵Thorsten von Stein is an employee of Roche Diagnostics.

⁶Claus Christiansen is the CEO of the Center for Clinical and Basic Research and served as an ad hoc consultant for Beigis Escu-Vesco, Boehringer Mannheim, Chiesi, Croupe Fournier Roche, Eli Lilly, MSD, Novo Nordisk, Pfizer, Procter and Gamble, Sandoz (now Novartis), and Wyeth-Ayerst. Dr. Christiansen also is the founder and board member of Osteometer Biotech A/S.

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not approved in the United States). Ibandronate is a new potent nitrogen-containing bisphosphonate that inhibits bone resorption in animal models at doses considerably lower than other bisphosphonates, for example, with twice the potency of risedronate and 10 times the potency of alendronate.⁽²⁾

Bisphosphonates are poorly absorbed from the gastrointestinal (GI) tract (<1%), and the absorption is decreased further by concomitant food intake. Therefore, oral bisphosphonates should be taken with water at least 30 minutes before breakfast to achieve sufficient absorption. This rigid dosing schedule is very inconvenient, particularly if patients are elderly, on concomitant medications, and/or have a busy daily schedule, and may lead to poor long-term adherence to therapy and jeopardize efficacy. Because bisphosphonates are not metabolized and bind strongly for prolonged periods to areas of active bone resorption, it is conceivable that the proven efficacy with rigid daily dosing can be achieved also with an intermittent cyclical therapy. Preclinical studies with ibandronate comparing daily and intermittent treatment regimens with the same total dose per study duration have shown equivalent results in terms of prevention of bone loss and architectural deterioration.^(3,4) In ovariectomized monkeys, intermittent therapy with ibandronate every 30 days also indicated a dose-dependent prevention of bone loss and architectural deterioration.⁽⁵⁾ Thus, there is evidence suggesting that a more convenient intermittent treatment schedule with ibandronate, offering a longer therapy-free interval, would provide equivalent efficacy to daily oral dosing. In addition, a previous study investigating intermittent once weekly bisphosphonate treatment has indicated that bone mineral density (BMD) increases similar to once daily regimens.⁽⁶⁾

The aim of this study was to investigate the efficacy and safety of intermittent oral administration of 20 mg of ibandronate compared with continuous daily oral administration of 2.5 mg of ibandronate and matching placebo.

MATERIALS AND METHODS

Study population

The study was a monocenter, double-blind, placebo-controlled randomized trial. Postmenopausal women were recruited ($n = 240$) who were aged 55–76 years, at least 5 years after menopause, and with low BMD at the spine (L2–L4) and/or the femoral neck (T score below -2.5 SD). Women with diseases or disorders known to influence bone metabolism such as liver disease, malignant disease, chronic alcoholism, primary hyperthyroidism, active thyroid disease, Paget's disease, and osteomalacia were excluded. Additional exclusion criteria included women treated within 6 months before the study with medications known to influence the bone metabolism (corticosteroids, female sex hormones, calcitonin, and cyclosporin) or women treated with fluoride within 12 months before the study or for a duration of 2 years as well as women previously treated with a bisphosphonate. Patients with renal impairment (serum creatinine, $>210 \mu\text{M}$ [equivalent to 2.4 mg/dl]) were excluded also. No attempt was made to exclude women because of

previous or active GI illnesses, unless they had the potential to influence bone metabolism (e.g., Crohn's disease or ulcerative colitis) or because of use of medications associated with GI intolerance, such as nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, H2 antagonists, or proton pump inhibitors.

Study design and treatment

The women were randomized to three groups, of which two groups received ibandronate and the other received placebo. The treatment regimens given were either continuous therapy with 2.5 mg of ibandronate daily ($n = 81$) or intermittent cyclical therapy with 20 mg of ibandronate every other day for the first 24 days out of every 3 months, followed by a 9-week period without active drug ($n = 78$). Thus, the dose of ibandronate was 225 mg over a 3-month period in the continuous group (assuming that each month has 30 days) and 240 mg in the intermittent group. The placebo group (total, $n = 81$) received placebo for 12 months and was subsequently switched to receive ibandronate, either continuously ($n = 37$) or intermittently ($n = 35$), for an additional 12 months.

Ibandronate was taken after at least 6 h of fasting in the morning with one glass of water immediately after awakening and at least 1 h before breakfast. No concomitant medication was taken together with the study medication. All patients received a daily dose of 400 IU of vitamin D and 500 mg of calcium. Both vitamin D and calcium were taken in the evening. During the 24-month study period, BMD was measured at baseline and every three months thereafter. Blood and urine sampling were conducted at 1-, 2-, 3-, 6-, 9-, 10-, 11-, 12-, 15-, 18-, 21-, and 24-month visits. The biochemical response to the intermittent and continuous therapy was recorded monthly during the first and the fourth 3-month treatment cycle. Urine and blood samples were collected in the morning between 7:30 and 10:30 a.m. after an overnight fast. Physical examinations were performed at baseline and final visit, and safety assessments such as vital signs, hematology, and safety laboratory tests were performed at each visit. Adverse events (AEs) and concomitant medication were recorded at each visit. Compliance was assessed every 3 months. Lumbar spine radiographs for the identification of vertebral fractures were not taken. Patients gave written informed consent before entering the study, which was conducted according to the Declaration of Helsinki and was approved by the local ethics committee and the health authorities.

Methods

Bone densitometry: BMD was measured by dual-energy X-ray absorptiometry (DXA) at the spine, hip, and distal forearm with a Hologic QDR2000 (Hologic, Waltham, MA, USA). The precision errors for BMD measurements at different skeletal sites ranged from 0.9% to 2.0%.

Biochemical parameters: Serum osteocalcin (OC) was measured by N-MID ELISA (Osteometer Biotech, Roskilde, Denmark). The inter- and intra-assay variations were both below 7%.⁽⁷⁾ Bone-specific alkaline phosphatase

TABLE 1. PATIENT BASELINE CHARACTERISTICS PER TREATMENT GROUP

	Matching placebo (n = 81)		2.5 mg of Ibandronate daily (n = 81)		30 mg of Ibandronate intermittent (n = 78)	
	Mean	SD	Mean	SD	Mean	SD
Age (years)	66.3	4.8	66.8	4.9	67.0	5.0
Height (cm)	160.0	6.0	160.4	6.2	160.7	5.9
Weight (kg)	62.6	9.5	62.7	8.3	63.8	9.9
Years since menopause	17.8	6.7	18.8	6.8	18.8	6.9
Baseline spinal BMD (L2-L4; g/cm ²)	.727	.074	.738	.060	.727	.061
Baseline spinal BMD (L2-L4; T score)	-3.264	.579	-3.206	.485	-3.232	.573
Baseline femoral neck BMD (g/cm ²)	.591	.079	.596	.070	.582	.065
Baseline femoral neck BMD (T score)	-2.987	0.630	-2.941	0.487	-3.083	0.425
Baseline u-CTX/Cr (μ mol/ml)	304.0	117.2	303.1	135.3	307.6	207.8
Baseline u-NTX/Cr (nmol/liter)	68.98	35.98	65.79	37.80	74.06	72.23
Baseline serum osteocalcin (ng/ml)	29.77	8.14	30.61	7.13	31.20	8.28
Baseline B-ALP (U/liter)	52.47	21.03	52.03	21.67	51.80	24.49
Baseline serum PTH (pmol/l)	4.180	1.852	4.207	1.771	4.441	2.364

(B-AP) was measured by the Iso-ALP (Roche Diagnostics, Mannheim, Germany). The inter- and intra-assay variations were below 5%.⁽⁹⁾ Urinary C-telopeptide of type I collagen (CTX/Cr) was measured by CrossLaps ELISA (Osteometer Biotech) and corrected for urinary creatinine. The inter- and intra-assay variations were <5% and <7%, respectively.⁽⁹⁾ Urinary N-telopeptide of type I collagen (NTX/Cr) was measured by Osteomark ELISA (Ostex International, Seattle, WA, USA). The inter- and intra-assay variations were <8% and <9%, respectively.⁽¹⁰⁾ Safety laboratory parameters included complete blood count, serum GO-transaminase (GOT), GP-transaminase (GPT), ALP, serum creatinine, and electrolytes (Ca, K, and Na).

Statistical analyses

The primary efficacy parameter was the percentage of change in BMD at the lumbar spine (L2-L4) relative to baseline. As predefined by the study protocol, efficacy was analyzed nonparametrically by a closed test procedure and preordering of hypotheses as follows. A test for superiority of the ibandronate treatment groups versus placebo was performed on 12-month data. Both ibandronate treatment groups were compared pairwise with the placebo-treated group by means of the Wilcoxon rank sum test after a simultaneous comparison of all three groups by means of the Kruskal-Wallis test had shown statistical significance ($\alpha = 5\%$).

After 24 months, the continuous and the intermittent ibandronate treatment groups were compared by means of an equivalence test using the two-sided 95% CI (Hodges-Lehmann estimate) of the median difference between the groups. Equivalence was concluded for the limits of this interval within the predefined tolerance region of $\pm 2\%$.

According to the closed test principle and preordering of hypotheses, each test was carried out at a level of $\alpha = 5\%$. A prerequisite for the performance of the equivalence test at the end of the study was that statistical significance differences to placebo at 1 year be shown first.

The superiority compared with placebo was investigated by carrying the last observed values forward until the end of the first year. The per protocol analysis presented in this article is the more stringent and preferred method for assessing equivalence between the two ibandronate regimens at the end of the study. The per protocol population was defined to allow for the most realistic estimation of the effect of ibandronate. An intent-to-treat (ITT) analysis was performed also and the results are similar to that of the per protocol (PP) analysis. Patients were excluded from the per protocol subset for various reasons, including insufficient compliance (<80% between successive visits) or for receiving medications not allowed per the protocol. The allocation of the patients to the per protocol and intent-to-treat population was done before the randomization code was broken. One hundred eighty-six patients were available for the per protocol analysis (continuous, intermittent, and placebo arms, 64, 60, and 62 patients, respectively). All patients randomized were included in the evaluation of safety.

RESULTS

Two hundred forty postmenopausal women were included in the study; 208 completed the first year of treatment and 188 completed the second year of treatment. Table 1 gives the baseline patient characteristics by treatment group. The groups were comparable concerning the demographic characteristics as well as in baseline BMD and biochemical markers of bone remodeling. The patient disposition throughout the 24 months and reasons for withdrawals are given in Table 2.

BMD at the spine

Baseline spinal BMD T score is given in Table 1. On the average, it was below -3.2 and comparable in all groups. BMD increased significantly at the spine (based on a per protocol population at 24 months) in both ibandronate-treated groups compared with baseline. All results are re-

TABLE 2. PATIENT DISPOSITION AND REASONS FOR WITHDRAWAL DURING 24 MONTHS OF IBANDRONATE THERAPY

Group	Matching placebo	2.5 mg of ibandronate continuously	20 mg of ibandronate intermittently
Patients randomized	81	81	78
Premature withdrawals during first 12 months	9	12	12
AEs	7	10	10
Voluntary withdrawal	1	2	1
Death	1	0	1
Patients continuing for the full 24 months	72	69	66

	2.5 mg ibandronate continuously	20 mg ibandronate intermittently		
No. of placebo patients switched over to ibandronate	37	35		
Premature withdrawals during second 12 months	4	6	4	5
AEs	2	2	4	4
Voluntary withdrawal	1	1	0	0
Death	0	2	0	1
Protocol violation	1	1	0	0
Patients completed	33	29	65	61

ported as ($\pm$ SEM) in Fig. 1. At 12 months, BMD at the lumbar spine had increased by +4.90% ($\pm$ 0.39) in the continuous group and by +4.84% ($\pm$ 0.46) in the intermittent group. In the total placebo group, BMD increased by +1.58% ($\pm$ 0.52). The differences between any of the two ibandronate groups and the placebo group were statistically significant after 12 months (two-sided Wilcoxon rank sum test; $p < 0.01\%$ for ITT as well as PP).

By 24 months, the BMD increase in the continuous group was +5.54% ($\pm$ 0.53) and in the intermittent group was +5.64% ($\pm$ 0.53) versus baseline. At 24 months, BMD in those patients switched to either continuous or intermittent ibandronate treatment increased to levels similar to those of the two groups that had received treatment for the full study period (Fig. 1). The increase of BMD at the spine is statistically equivalent in the two groups of patients who received 2 years of ibandronate either continuously or intermittently. The 95% CI for the Hodges-Lehmann estimate of the difference between the two treatment groups ranges from -1.82% to +1.32%, which is within the predefined limit of 2.0% of therapeutical equivalence. Statistical equivalence also could be shown in the ITT analysis.

BMD at the hip

At 24 months, the increase in BMD at the trochanter was +4.59% ($\pm$ 0.51) and +4.72 ($\pm$ 0.56) for the continuous and the intermittent groups, respectively, in the per protocol population, versus baseline. BMD at the total hip increased by +3.41% ($\pm$ 0.40) and +3.35% ($\pm$ 0.40), respectively, versus baseline. (Fig. 2). As at the spine, the pattern of BMD increases at the hip sites is very similar between the two treatment groups during both the first and the second 12 months. BMD in the placebo group increased <1% over 12 months at the total hip.

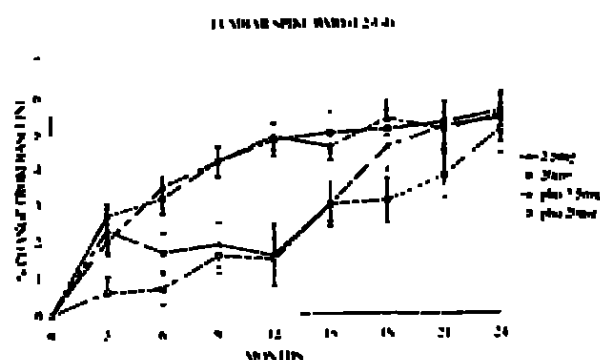


FIG. 1. Changes over time given in percent of baseline values in BMD at the lumbar spine in the three treatment groups (per protocol, mean $\pm$ SEM).

Baseline femoral neck T score was about -3.0 and virtually similar in all groups (Table 1). In the continuous group, femoral neck BMD increased by 2.90% ($\pm$ 0.59) over 24 months (mean $\pm$ SEM). The number was 2.28% ($\pm$ 0.58) in the intermittent group. The placebo groups had slight increases in the first 12 months. When the placebo groups were switched to ibandronate in the following 12 months, they reached the level of the two groups that had received treatment for 24 months.

Biochemical markers

Figure 3 presents the changes in biochemical markers of bone resorption and formation during the full treatment period based on per protocol. All results are reported as mean ($\pm$ SEM). At 24 months, the urinary concentrations of

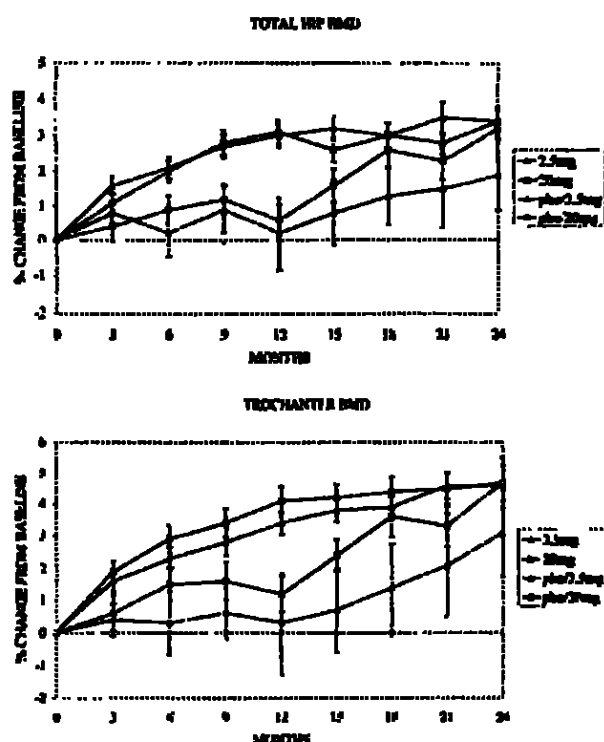


FIG. 2. Changes over time given in percent of baseline values to BMD at the total hip and trochanter in the three treatment groups (per protocol, mean $\pm$ SEM).

creatinine-corrected CTx were clinically significantly reduced by -58.8% (± 4.5) and -44.2% (± 5.9), respectively, in the continuous and intermittent groups compared with baseline. Urinary (creatinine corrected) NTx was clinically significantly reduced by -60.5% (± 3.5) and -49.8% (± 5.4), respectively. The intermittent group showed a more variable response throughout the treatment period. The maximal suppression was only apparent at month 1 and month 10 when urine was sampled soon after drug intake, showing the immediate response to the drug (measured monthly during the first and the fourth treatment cycle). The continuous group had a more constant response in both resorption markers. A plateau was reached at approximately 3 months and the pattern did not change significantly for the remaining treatment period. The serum concentrations of OC and B-ALP in the continuous and intermittent group decreased at a slower rate and to a smaller extent than did the bone resorption markers. A plateau was reached at 6–9 months at a level of approximately -40% for both groups. At 24 months, OC had decreased by -51.5% and -49.1% and B-ALP had decreased by -38.1% and -32.0% , respectively, in the continuous and intermittent group. In the placebo group, OC decreased by -13.8% and B-ALP by -12.4% . After crossed over to treatment, the level of reduction in the second year was similar to that of the two groups treated for 24 months. Although both ibandronate treatment groups showed a statistically significant difference in bone marker levels relative to placebo at 12 months,

no difference was observed between the two active treatment groups.

As shown in Fig. 4, the serum parathyroid hormone (PTH) values were slightly increased during the first treatment year in the two ibandronate groups. Two peak increases were observed in the intermittent group at the time when blood was sampled to detect the immediate effects of the intermittent ibandronate administration. The elevated serum PTH did not result in any pathological serum PTH or serum calcium values and PTH had returned to normal by 12 months after commencement of treatment.

Safety and tolerability

Eleven⁽¹¹⁾ of the 240 women who were randomized had a documented medical history of previous GI disease. During the first 12 months, 43 women (18%) had some intake of NSAIDs, that is, 12 (15%) in the continuous group, 13 (17%) in the intermittent group, and 18 (22%) in the placebo group. During the second year, 41 (20%) of the 207 women, who continued after one year) had some intake of NSAIDs, that is, 13 (19%) in the continuous group, 15 (23%) in the intermittent group, and 9 + 4 (18%) in those who switched from placebo to active treatments. Figure 5 gives an overview of the AEs including GI AEs during the first 12 months in the two ibandronate-treated groups compared with placebo. Overall, there were no differences between the groups. During the first 12 months, the ibandronate-treated groups showed a numerically higher incidence of diarrhea compared with the placebo groups. The incidence of diarrhea was lower during the second year.

DISCUSSION

Successful treatment of osteoporosis with bisphosphonates ideally requires a drug with proven antifracture efficacy and long-term patient adherence. Despite their proven efficacy in significantly increasing BMD and reducing fractures at all clinically relevant sites, the use of oral bisphosphonates is inconvenient, especially for patients with busy daily schedules. Thus, bisphosphonates must be taken fasting, with a full glass of water while remaining upright for at least 30 minutes before intake of any food or beverage other than water. Bioavailability is reduced substantially if patients do not adhere to this dosing regimen. In addition, oral daily bisphosphonates have been associated with GI AEs.^(12,13) The drawbacks of the strict dosing regimen may be overcome by reducing the frequency of drug intake. Thus, studies have been conducted to assess intermittent regimens, such as once weekly alendronate.⁽⁶⁾ Furthermore, preclinical data with ibandronate provided evidence that a total dose administered over a defined period provides equivalent results irrespective of the dosing schedule, providing that the dose used is efficacious.^(7,8) Although the precise mechanisms underlying the efficacy of intermittent therapy has not been elucidated fully, contributing factors may include the high affinity of bisphosphonates to bone and the prolonged effect they exert after having been absorbed onto the bone surface. This prolonged effect appears

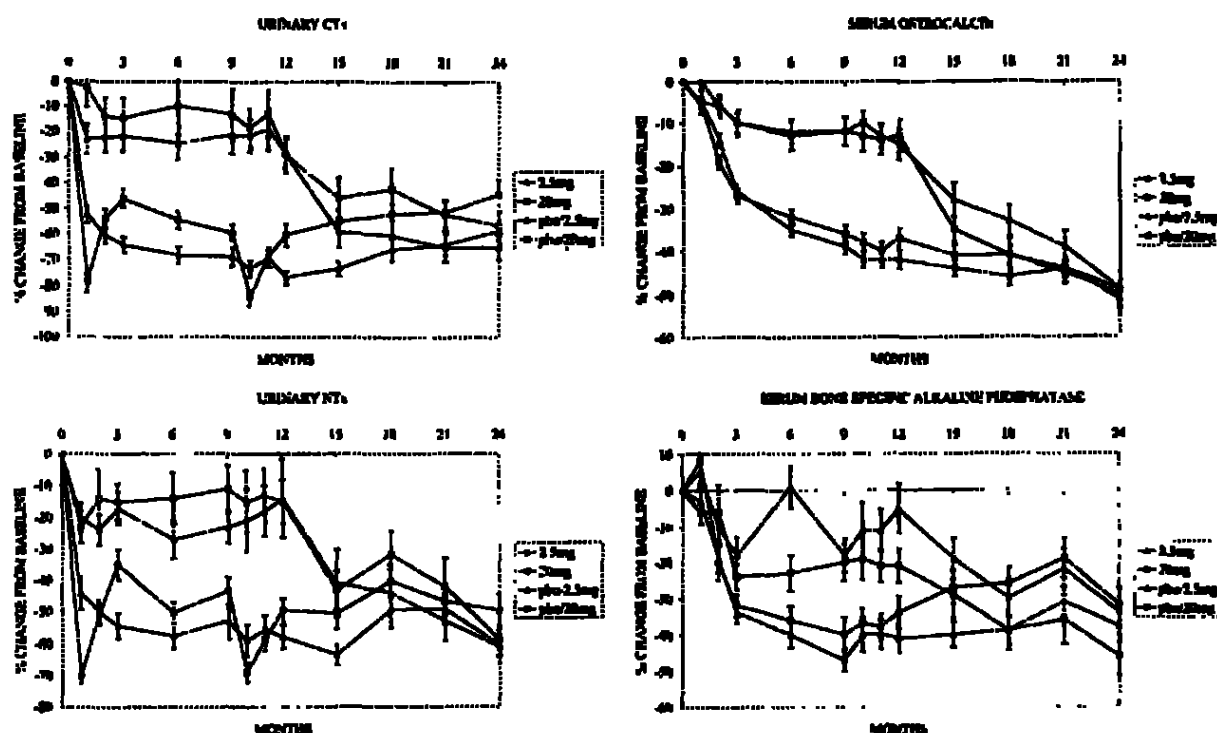


FIG. 3. Changes over time in the markers of bone turnover given in percent of baseline (per protocol, mean $\pm$ SEM). CTx and NTx are markers of bone resorption and OC and B-ALP are markers of bone formation.

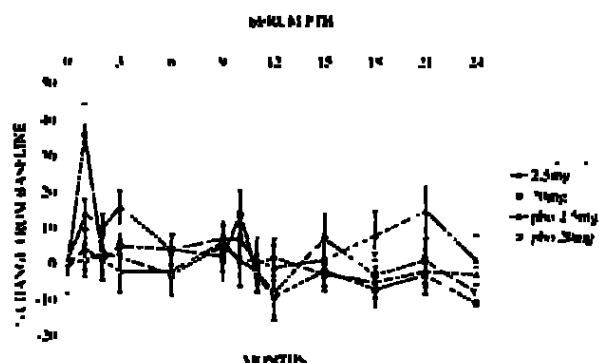


FIG. 4. Changes over time in serum PTH concentrations given in percent of baseline (per protocol, mean $\pm$ SEM).

to remain even after therapy discontinuation.⁽¹¹⁾ This was shown also in a study with oral ibandronate given daily for 12 months (2.5 mg), in which bone resorption decreased significantly and only returned to baseline 12 months after treatment withdrawal.⁽¹⁴⁾

In this study, ibandronate was given either continuously as 2.5 mg daily or intermittently as 20 mg every other day for 24 days at the beginning of every 3 months, followed by a 9-week period without active drug. The daily dose of 2.5 mg was selected based on a phase II study showing that 2.5 mg/day is the minimal dose that provides maximal effects (equivalent of 5 mg/day) and with a decrease of bone

resorption markers of about 60–70% and a decrease of bone formation markers of about 40%.⁽¹³⁾ This corresponds to a normalization of bone remodeling to a premenopausal level. The intermittent dosing regimen was selected based on preclinical results.^(15,16) The two dosing regimens used in this study provide similar total dosing during each 3-month period.

In this study, the increase in lumbar spine BMD at 12 months was +4.90% and +4.84% compared with baseline in the continuous and intermittent groups, respectively. Both ibandronate-treated groups had statistically equivalent increases in BMD, supporting previous studies showing that it is the total dose and not the dosing regimen that is important for efficacy.⁽¹⁶⁾ BMD continued to increase during the second 12 months, reaching +5.54% and +5.64%, respectively, for the continuous and intermittent treatment groups. These increases in BMD are in the range of those seen with other N-containing bisphosphonates.⁽¹⁷⁾ The majority of the BMD effect was reached within 12 months of treatment. This also would be expected from the dynamics of bone remodeling. However, given the statistical variation with the relatively small sample size, the data are compatible with a continued, albeit slowed, BMD increase in the second year, similar to what was observed in other bisphosphonate studies.^(18,19)

In the continuous group, the reduction in bone resorption markers reached a plateau at approximately 60 to 70%, respectively, which was maintained throughout the 24-month treatment period. In the intermittent group, bone

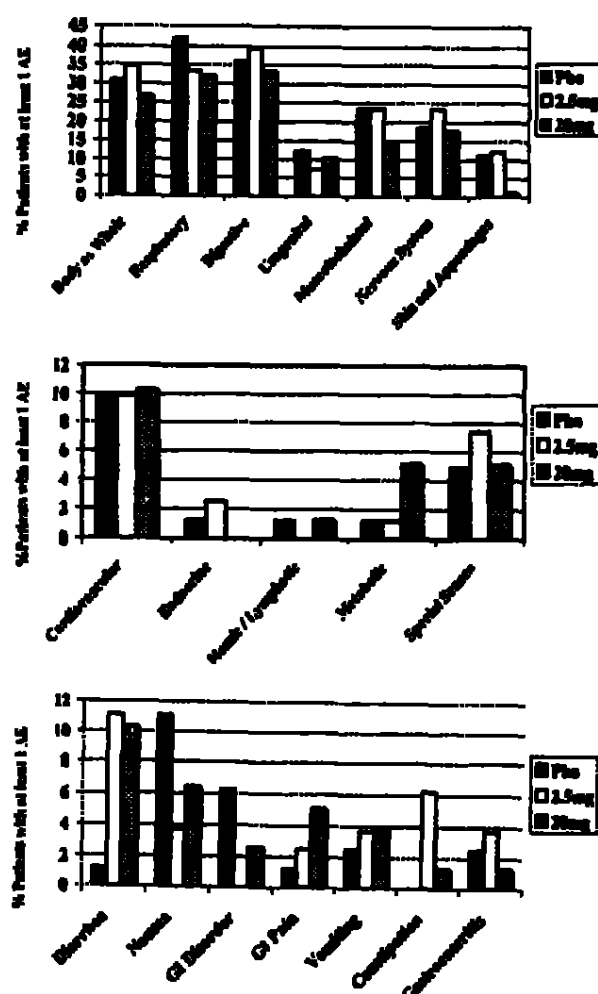
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FIG. 5. AEs according to total body system (top and middle) and digestive system (bottom) within the first 12 treatment months. Data are presented as patients with at least 1 AE (ITT).

resorption markers were reduced to a similar level despite the fact that the 9-week interval without active drug is considerably longer than the life span of the osteoclast (± 3 weeks).⁽²⁶⁾ However, the pattern of suppression was more variable, with maximum decreases 1 month into each treatment cycle as shown by the measurements conducted monthly during the first and fourth treatment cycle. This pattern is expected because patients received their full quarterly dose within the first month of each treatment cycle. The measurements at the end of the 3-month treatment schedule reflect the residual effect before the next treatment cycle. Despite this apparent variable bone marker pattern in the intermittent group, the increases in BMD observed in the intermittent therapy are equivalent to that of daily therapy. These results confirm the preclinical data showing that it is the total dose over a predefined period and not the dosing regimens that is the determining factor for effect on bone mass and architecture after ibandronate treatment.

In the placebo group, the markers of bone resorption u CTX/u Creat. and u NTX/u Creat. decreased by

-28.4% (± 4.4) and -14.2% (± 7.2) at 12 months. When these patients were subsequently switched to ibandronate, the level of bone markers suppression at 24 months was similar to that seen in the ibandronate-treated groups.

Ibandronate was well tolerated, and no safety concerns were identified. The incidence of AEs was similar in both ibandronate-treated groups and in the placebo groups. In view of the lack of serious GI side effects in a population in which GI disease had not been specifically exempted, these findings hold promise of a good tolerability and safety profile of ibandronate. This trial showed an increased incidence of diarrhea in the participants receiving ibandronate. Because of the small number of patients in this study, this may represent a chance finding. The large long-term phase III trials will confirm whether this is a drug effect or a random finding.

In conclusion, this trial showed that intermittent ibandronate is as effective as the continuous treatment in terms of significantly increasing BMD at the spine and hip and suppressing markers of bone turnover. The anti-fracture efficacy of intermittent treatment regimens with ibandronate needs to be confirmed in large prospective trials. These results support the development of new ibandronate dosing regimens designed to minimize the dosing frequency and aimed at enhancing patient acceptance and compliance with long-term treatment.

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Möckel et al.

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

[54] ORAL PHARMACEUTICAL PREPARATION
CONTAINING IBANDRONAT[75] Inventors: Jörn Möckel, Heidelberg; Rolf-Dieter
Gabel, Schwetzingen; Heinrich Wong,
Laudenbach, all of Germany[73] Assignee: Roche Diagnostics GmbH, Mannheim,
Germany[*] Notice: This patent issued on a continued pro-
secution 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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[58] Field of Search 424/480, 482

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[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

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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 limitations.

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
Macrogel	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
Macrogel	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
Macrogel	0.40	0.40	0.40
Ethyl methyl methacrylate copolymer*	0.04	0.04	0.04
Polyacrylic	0.04	0.04	0.04
Total film coated	5.44	5.44	5.44

*Employed in the form of Emulphor® NE 30 D as an aqueous dispersion.

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

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EXAMPLE 4

Ibandronate-containing core:	
Ibandronate dose [mg] in 86 mg tablet core:	10
Ibandronate-free coat [mg]:	
Macrogel	37.844
White clay	8.138
Talc	1.000
Macrogel	2.844
Choline syrup	2.035
Titanium dioxide	1.638
Polyvidone	0.407
Monomethyl glycol wax	0.300
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
Form of coat:	7 mm in diameter, plain, with fracture
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:

- about 51.425% by weight of methylhydroxypropylcellulose;
- about 24.650% by weight of titanium dioxide;
- about 15.000% by weight of polyethylene glycol; and
- 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.