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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Re.: Código 011-378-444
Expediente No. 11-52.660
Fase nacional de Solicitud
de Patente PCT
LABORATORIOS LICONSA, S.A.

En relación con el expediente de la referencia y dando cumplimiento a la última providencia recaída sobre este asunto por medio del presente escrito me permito manifestarles lo siguiente:

1. Siguiendo precisas instrucciones de mi representada modifíco el título de esta solicitud como sigue

**PARTICULAS INHALABLES QUE COMPRENDEN UNA FORMA ANHIDRA AMORFA
DE TIOTROPIO ESTABILIZADA CON UN AGENTE ESTABILIZANTE QUE ES UN
DERIVADO DE AZUCAR, COMPOSICIONES FARMACEUTICAS QUE LAS
CONTIENEN Y PROCEDIMIENTO PARA SU PREPARACION**

2. Se adjunta un nuevo capítulo reivindicatorio, el cual ha sido revisado y modificado.

La nueva reivindicación 1 se refiere a partículas inhalables donde el porcentaje de bromuro de tiotropio en peso referido al peso de bromuro de tiotropio y agente estabilizante está comprendido entre 0.1-10% y donde el derivado de azúcar se selecciona del grupo que consiste en monosacáridos, disacáridos, oligo y polisacáridos y polialcoholes. La nueva reivindicación 2 se refiere a partículas inhalables donde el porcentaje de bromuro de tiotropio en peso referido al peso de bromuro de tiotropio y agente estabilizante está comprendido entre 4-8%. Las reivindicaciones 1 y 2 modificadas tienen base en la página 8, líneas 24-27 y página 9, líneas 13-15 de la solicitud presentada.

Las reivindicaciones 3-7 no se han modificado y las reivindicaciones 8-9 que estaban en trámite se han eliminado.

Las nuevas reivindicaciones 8-9, correspondientes a la reivindicaciones 10 y 11 que estaban en trámite, se refieren a una composición farmacéutica. Esta modificación, que tiene base en la reivindicación 12 original, se ha realizado para clarificar que la mezcla de las partículas inhalables de las reivindicaciones 1-7 con excipientes de formulación tales como excipientes gruesos es una composición farmacéutica. La reivindicación 14 nueva, correspondiente a la reivindicación 17 que estaba en trámite, se ha adaptado para incorporar la modificación de estas reivindicaciones.

Las nuevas reivindicaciones 10-15 corresponden a las reivindicaciones 13-18 que estaban en trámite.

La reivindicación 19, relativa al uso de las partículas, ha sido también eliminada.

3. El examinador considera que "las reivindicaciones 1 - 11 relativas a "partículas inhalables" no son claras porque, a la luz de lo indicado en la memoria, deberían corresponder a una "composición farmacéutica" y sugiere modificarlas para que se refirieran a composiciones farmacéuticas.

El solicitante discrepa del examinador por los motivos siguientes.

- Generalmente, las sustancias activas por sí mismas no pueden ser fácilmente absorbidas por el cuerpo humano, por lo que necesitan ser administradas en forma de una composición farmacéutica apropiada que contenga la sustancia activa y uno o más excipientes farmacéuticamente aceptables. Dichos excipientes facilitan la preparación, conservación y administración de la sustancia activa y normalmente son sustancias inertes, es decir, no tienen efecto farmacológico.

Tal como se indica en la memoria, las composiciones de la invención son útiles en el tratamiento de las enfermedades respiratorias, en particular la enfermedad pulmonar obstructiva crónica (EPOC) y el asma.

En la presente invención la sustancia activa con efecto farmacológico está en forma de partículas que comprenden una forma anhidra amorfa de bromuro de tiotropio estabilizada con un agente estabilizante que es un derivado de azúcar, donde el porcentaje de bromuro de tiotropio en peso referido al peso de bromuro de tiotropio y agente estabilizante está comprendido entre 0.1-10% tal como se indica en la reivindicación 1. Estas características resultan en partículas inhalables. El derivado de azúcar de las partículas de la reivindicación 1 no es un excipiente para formular la composición farmacéutica final, sino que es un agente estabilizante que permite conseguir partículas estabilizadas de tiotropio.

- En el caso concreto de las enfermedades respiratorias donde la sustancia activa se administra por inhalación, ocurre con frecuencia que las partículas microfinas tienden a desarrollar una fuerte adhesión y cohesión que a su vez genera propiedades reológicas deficientes y agregación del polvo. Por esta razón, en algunos casos, es necesario formular dichas partículas con un excipiente grueso que mejore su fluidez. La composición farmacéutica reivindicada en la reivindicación 8, se refiere a las partículas inhalables que comprenden una forma anhidra amorfa de bromuro de tiotropio estabilizada con un agente estabilizante y excipientes de formulación tal como los excipientes gruesos mencionados anteriormente. De lo anterior queda claro que las partículas inhalables (sustancia activa) de las reivindicaciones 1-7 y las composiciones farmacéuticas de las reivindicaciones 8-12 son aspectos diferentes de la invención.

En opinión de la sociedad solicitante, puesto que las partículas inhalables de la reivindicación 1 son claras, y cumplen con los requisitos de novedad y nivel inventivo, tal como se demuestra a continuación, la modificación de las partículas inhalables de la reivindicación 1 por composiciones farmacéuticas sería una limitación injusta del alcance de protección de las reivindicaciones.

4. El examinador objeta la claridad de la reivindicaciones 4, 7 y 10 (que corresponden con las nuevas reivindicaciones 4, 7 y 8) porque considera que los términos "con un tamaño aerodinámico medio de partícula de hasta 10 μm ", "secadas por atomización" y "que presentan un tamaño de partícula medio de 15 a 250 μm " son un resultado a alcanzar y no definen las partículas inhalables.

Mi representada discrepa del examinador por los motivos siguientes.

- La reivindicación 4 se refiere a partículas inhalables con un tamaño aerodinámico medio de partícula de hasta 10 μm . En opinión de la solicitante, la expresión "con un tamaño aerodinámico medio de partícula de hasta 10 μm " no define un resultado a alcanzar sino que define una característica física de las partículas, su tamaño.

Tal como se desprende de la memoria, en este caso, el resultado a alcanzar es que las partículas sean inhalables, es decir que las partículas sean adecuadas para que penetren en los pulmones y puedan desarrollar una actividad sistémica opcionalmente a través de los alvéolos. El tamaño aerodinámico medio de partícula de hasta 10 μm es una solución técnica que proporciona el resultado al problema de obtener partículas que sean inhalables. Además, la memoria indica cómo se puede medir el tamaño de partícula aerodinámica (ver ejemplo evaluación aerodinámica in vitro).

- La reivindicación 7 se refiere a partículas inhalables secadas por atomización. Mi representada considera que la expresión "secadas por atomización" no define un



resultado a alcanzar, sino que define el procedimiento por el cual se han obtenido las partículas.

En este caso, el resultado a alcanzar es que las partículas estén estabilizadas, tanto físicamente como químicamente. El procedimiento de secado por atomización es una solución técnica que proporciona el resultado al problema de obtener partículas que estén estabilizadas.

- Por último, la reivindicación 8, que corresponde a la reivindicación 10 anterior, se refiere a partículas inhalables que están mezcladas con uno o más excipientes gruesos que presentan un tamaño de partícula medio de 15 a 250 μm . En nuestra opinión, la expresión "que presentan un tamaño de partícula medio de 15 a 250 μm " no define un resultado a alcanzar, sino que define una característica física de los excipientes gruesos, en particular, su tamaño.

Tal como se desprende de la memoria, en este caso, el resultado a alcanzar es mejorar la fluidez de las partículas inhalables. Esto se consigue con el uso de excipientes gruesos, los cuales deben tener un tamaño de partícula que los haga no inhalables, ya que las partículas microfinas tienden a desarrollar una fuerte adhesión y cohesión que puede conllevar desventajas. Por ello, el uso de uno o más excipientes gruesos con un tamaño de partícula medio de 15 a 250 μm es una solución técnica ventajosa que proporciona el resultado al problema de obtener partículas con una fluidez mejorada.

5. Con relación a las anterioridades citadas por el Despacho, a continuación se presentan las consideraciones de la solicitante dirigidas a desvirtuar los argumentos presentados en el concepto técnico.

a. Novedad

Reivindicación 1

El Examinador considera que la reivindicación 1 no es nueva a la vista del documento D1. La nueva reivindicación 1 se refiere a partículas inhalables que comprenden una forma anhidra amorfa de bromuro de tiotropio estabilizada con un agente estabilizante que es un derivado de azúcar; donde el % de bromuro de tiotropio en peso relativo al peso del bromuro de tiotropio y agente estabilizante está comprendido entre 0,1-10%.

El documento D1 describe cápsulas para inhalación que contiene el principio activo tiotropio en forma de preparaciones en polvo (D1, página 2, líneas 3-5).

El tiotropio puede encontrarse en forma cristalina o amorfa (D1: página 6, líneas 44-45). Adicionalmente, el polvo inhalable contenido en las cápsulas de inhalación contiene, además del principio activo, al menos un excipiente que consiste en una fracción uniforme en cuanto al tamaño medio de partícula del excipiente, o en una mezcla de un excipiente grueso (de tamaño medio de partícula de 15-80 micras) y un excipiente fino (de un tamaño medio de partícula de 1-9 micras) (D1: página 4, líneas 34-38). El excipiente puede ser un disacárido tal como lactosa (D1: página 5, líneas 2-4).

Sin embargo, el documento D1 no describe partículas anhidras tales como las englobadas en la presente reivindicación 1.

Por otro lado, el polvo inhalable descrito en D1 se obtiene mediante un procedimiento de mezcla mecánica, en el cual el principio activo (tiotropio) se mezcla físicamente con el excipiente o mezcla de excipientes en un contenedor de mezcla adecuado (D1: página 6, líneas 6-7). En un procedimiento de mezcla mecánica tal como el que se describe en D1 ni el tamaño de partícula ni la forma física del principio activo deberían verse alteradas. Esto significa que, en la mezcla final que contiene tiotropio y excipientes, el tamaño de partícula, así como la forma física del principio activo, deberían ser los mismos que antes de llevar a cabo la correspondiente mezcla.

En los ejemplos de D1, el material de partida utilizado es bromuro de tiotropio monohidrato cristalino micronizado, el cual se mezcla o bien con lactosa gruesa o bien con una mezcla de lactosa fina y gruesa. En este procedimiento no se añaden disolventes. Como consecuencia, la forma obtenida de tiotropio no puede encontrarse en forma anhidra. Más bien al contrario, en las tablas de los ejemplos 2-6 de D1 se indica que las cápsulas para inhalación contienen bromuro de tiotropio monohidrato y lactosa monohidrato.

En conclusión, el documento D1 no describe partículas anhidras y, por tanto, la reivindicación 1 cumple con el requisito de novedad frente a este documento.

b. Nivel Inventivo

Reivindicación 1

El documento D1 se puede considerar como el documento más cercano del estado de la técnica para la presente invención, ya que describe inhalable formulaciones que comprenden una mezcla de partículas de monohidrato de bromuro de tiotropio y lactosa.

Según la descripción de este documento, el ingrediente activo puede ser amorfo. Las formulaciones de D1 se preparan por mezcla física de los componentes.

Las partículas de la reivindicación 1 difieren de las de D1 en que en las partículas reivindicadas el ingrediente activo y el excipiente están en contacto directo. Esto significa que el tiotropio y el agente estabilizante están mezclados a nivel molecular.

En particular, las partículas reivindicadas pueden estar en la forma de una matriz que comprende el ingrediente activo dispersado molecularmente, o en forma de partículas del excipiente recubierto por una capa de ingrediente activo. En el primer caso, la estructura es el resultado del secado por atomización (spray-drying) de una solución de tiotropio y una solución de agente estabilizante, mientras que en el segundo caso, la estructura es el resultado del secado por atomización de una solución de tiotropio y una suspensión de agente estabilizante.

Esta diferencia entre las partículas reivindicadas y las de D1 tiene el efecto de estabilizar las partículas inhalables. Así, la presente invención resuelve el problema de proporcionar partículas inhalables que comprenden una forma amorfa y anhidra de tiotropio y agente estabilizante, que estén estabilizadas.

En un procedimiento de mezcla mecánica tal como el de D1, ni el tamaño de partícula ni la forma física del principio activo deberían verse alteradas. Esto significa que, en la mezcla final que contiene tiotropio y excipientes, el tamaño de partícula y la forma física del principio activo deberían ser las mismas que antes de llevar a cabo la correspondiente mezcla.

Así, partiendo de tiotropio en forma cristalina, que es la forma sólida más estable, y siguiendo las enseñanzas de D1, se obtiene una mezcla donde el principio activo está presente en la misma forma cristalina.

En el caso de partir de tiotropio en forma amorfa, siguiendo las enseñanzas de D1, sería esperable obtener tiotropio en forma amorfa. Sin embargo, dado que la forma amorfa es una forma termodinámicamente inestable y tiende a convertirse en la forma cristalina en el transcurso del tiempo, la forma amorfa en la mezcla final no estaría estabilizada. En realidad, la estabilidad del tiotropio amorfo en la mezcla final con los excipientes, tal como se obtiene mediante el procedimiento de mezcla mecánica de D1, sería comparable a la estabilidad de tiotropio amorfo puro. Y, como ya se ha demostrado en la invención en examen, el tiotropio amorfo puro es inestable (ver Figura 1 y página 21, líneas 5-11 de la presente solicitud).

Por tanto, el procedimiento de mezcla mecánica descrito en D1 no podría dar lugar a partículas inhalables que comprenden una forma amorfa anhidra estabilizada de tiotropio con un agente estabilizante.

Cabe señalar que, en la presente invención las partículas se obtienen mediante un proceso de secado por atomización (spray-drying). El secado por atomización es un

proceso de solidificación rápida y generalmente da lugar a materiales amorfos. En el caso de las partículas inhalables de la invención en examen, la naturaleza y el tamaño medio de partícula de las partículas inhalables obtenidas, que contienen tiotropio en contacto directo con un agente estabilizante (i.e., tiotropio y el agente estabilizante están mezclados a nivel molecular) se determinan después del procedimiento de secado por atomización. Así, las partículas resultantes después del secado por atomización están estabilizadas, tal como demuestran los ensayos de estabilidad (Figura 2 de la solicitud en examen).

Adicionalmente, el solicitante aporta un informe experimental en el que se demuestra lo anterior. En particular, en dicho documento se han preparado dos muestras que contienen tiotropio y lactosa por un procedimiento de mezclado mecánico, tal como el que se describe en D1. Los detalles de la preparación de estas dos muestras así como su análisis de difracción rayos X se proporcionan en el Anexo 2. La primera muestra, denominada en el informe experimental como MC14G2009-D2, se preparó mezclando físicamente lactosa cristalina y tiotropio cristalino. La segunda muestra, denominada como M14G2009-D2, se preparó mezclando físicamente lactosa cristalina y tiotropio amorfo.

Tras la preparación de las muestras, se registraron los difractogramas de rayos X de las mismas. Con el propósito de comparación, también se incluyó en el análisis de rayos X una muestra preparada según la presente invención. Esta muestra, denominada en el informe experimental como B23C2009, se preparó por secado por atomización de una solución de lactosa y tiotropio en etanol-agua. Como se puede ver en la figura 2 del anexo 2, el análisis de rayos X de la muestra según la invención (B23C2009) mostró un producto amorfo. En contraste, de acuerdo a la figura 4 del Anexo 4, el análisis de rayos X bajo las mismas condiciones de ambas muestras obtenidas por un procedimiento de mezclado mecánico, MC14G2009-D2 y M14G2009-D2, mostró en ambos casos productos cristalinos.

Por tanto, estos experimentos muestran que incluso en el caso de partir de tiotropio en forma amorfa, siguiendo las enseñanzas de D1 se obtiene un producto cristalino. Esto significa que la mezcla final no está estabilizada en forma de producto amorfo. En otras palabras, cuando el tiotropio y el agente estabilizante se mezclan en un estado no molecular (es decir, no están mezcladas en un estado molecular) no se obtiene ningún efecto de estabilización de la mezcla final como producto amorfo.

Además, las partículas obtenidas por un procedimiento de mezcla mecánica como el descrito en D1 y las partículas de la invención obtenidas mediante el secado por atomización son estructuralmente diferentes. Esto puede comprobarse a partir de las imágenes obtenidas en un microscopio electrónico de barrido (SEM) que se proporcionan

como Anexo 3. En particular, se registraron imágenes de SEM para las siguientes muestras:

1. Muestra comparativa obtenida por un proceso de mezclado mecánico, tal como el descrito en D1: **SPIRIVA**. Esta muestra corresponde al producto comercial SPIRIVA. Según la información de prescripción del producto Spiriva aprobada por la FDA: "Each light green, hard gelatin SPIRIVA capsule contains 18 mcg tiotropium (equivalent to 22.5 mcg tiotropium bromide monohydrate), blended with lactose monohydrate (which may contain milk proteins) as the carrier", es decir: "Cada cápsula verde claro de gelatina dura de SPIRIVA contiene 18 mcg de tiotropio (equivalente a 22,5 mcg de bromuro de tiotropio monohidrato) mezclado con lactosa monohidrato (que puede contener proteínas de la leche) como portador" (Anexo 4, página 4, punto 11, segundo párrafo).
2. Muestra obtenida por secado por atomización en forma de una matriz según la invención: **Tiotropium SD 702016**.
3. Mezcla de partículas secadas por atomización en forma de una matriz según la invención y excipiente grueso: **12TIO12011CP02F1i**.

De acuerdo con los resultados obtenidos, se puede concluir que la composición obtenida siguiendo las enseñanzas de D1 (muestra comparativa **SPIRIVA**) y las composiciones según la invención (**Tiotropium SD 702016** y **12TIO12011CP02F1i**) muestran claras diferencias en las estructuras de los productos. En particular:

- Se observa que la muestra comparativa SPIRIVA se compone de lactosa gruesa y pequeñas partículas de forma irregular que contienen de lactosa y tiotropio micronizado, mientras que
- Se observa que las muestras secadas por atomización según la invención (**Tiotropium SD 702016** y **12TIO12011CP02F1i**) se componen de lactosa gruesa y pequeñas partículas esféricas que contienen una matriz en la que el tiotropio está dispersado molecularmente.

Por otro lado, el documento D2 no aborda el problema de obtener una forma anhidra amorfa de tiotropio, que esté estabilizada.

En particular, el documento D2 se refiere a partículas de liberación pulmonar de un agente activo que comprende un fosfolípido y leucina (D2: página 2, párrafo [0017]). Como agente activo se cita "tiotropium" (D2: página 3, párrafo [0043]). Además del

agente activo, las partículas pueden incluir excipientes como la lactosa (D2: página 4, párrafo [0046], y página 15 párrafo [0178]). También describe que las partículas pueden ser amorfas, sustancialmente amorfas o cristalinas (D2: página 8, párrafo [0100]). D2 no indica ni sugiere que se pueda utilizar un derivado de azúcar como agente estabilizante.

Las formulaciones más próximas a la presente invención son las formulaciones D y H del Ejemplo 6. La formulación D comprende leucina, manitol, bromuro de ipratropio y xinafoato de salmeterol y la formulación H comprende leucina, maltodextrina, ipratropio, salmeterol y DMPE (fosfolípido). D2 no se refiere al problema de estabilizar una forma amorfa anhidra de tiotropio.

En conclusión en D1, sólo o en combinación con D2, no se describe ni sugiere que el secado por atomización de una combinación de tiotropio y un agente estabilizante en las proporciones reivindicadas podría producir partículas con una estabilidad mejorada del ingrediente activo (tanto química como física) en comparación con las partículas inhalables que contienen tiotropio amorfo puro.

En nuestra opinión, el experto en la materia no habría considerado obvio que el secado por atomización de una mezcla de tiotropio y un agente estabilizante en las proporciones reivindicadas resultaría adecuada para obtener tales partículas inhalables estabilizadas. Por todas las razones indicadas anteriormente, la reivindicación 1 cumple con el principio de nivel inventivo a la vista de D1 y D2.

Reivindicaciones 2-15

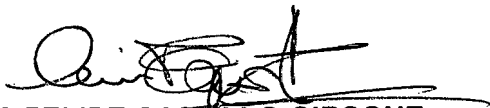
Todas estas reivindicaciones dependen directa o indirectamente de la reivindicación 1, la cual es nueva e inventiva. Por tanto, estas reivindicaciones también cumplen los requisitos de novedad y nivel inventivo.

6. Se acompaña también el comprobante de pago por concepto de exceso de reivindicaciones por valor de \$ 150.000.00, recibo No. 201690

7. Se adjunta también el formulario petitorio corregido y una nueva carátula.

Renuncio al término faltante de traslado, y les solicito otorgar el privilegio de patente de invención aquí tramitado.

De Ustedes Atentamente,


LUIS FELIPE CASTILLO GIBSONE
T.P. No. 68.995 del C.S.J.

REIVINDICACIONES

1. Partículas inhalables que comprenden una forma anhidra amorfa de bromuro de tiotropio estabilizada con un agente estabilizante que es un derivado de azúcar; donde el % de bromuro de tiotropio en peso relativo al peso del bromuro de tiotropio y agente estabilizante está comprendido entre 0,1-10% y donde el derivado de azúcar se selecciona del grupo que consiste en monosacáridos, disacáridos, oligo y polisacáridos y polialcoholes.
2. Partículas inhalables de acuerdo con la reivindicación 1, donde el % de bromuro de tiotropio en peso relativo al peso del bromuro de tiotropio y agente estabilizante está comprendido entre 4-8%.
3. Partículas inhalables de acuerdo con cualquiera de las reivindicaciones 1-2, donde el derivado de azúcar es lactosa.
4. Partículas inhalables de acuerdo con cualquiera de las reivindicaciones 1-3, con un tamaño aerodinámico medio de partícula de hasta 10 μm .
5. Partículas inhalables de acuerdo con cualquiera de las reivindicaciones 1-4, donde la forma amorfa del tiotropio estabilizada con el agente estabilizante comprende una matriz en la que el tiotropio está dispersado en un estado molecular.
6. Partículas inhalables de acuerdo con cualquiera de las reivindicaciones 1-4, donde la forma amorfa de tiotropio estabilizada con el agente estabilizante comprende tiotropio amorfo dispersado en la superficie del agente estabilizante.
7. Partículas inhalables de acuerdo con la reivindicación 1, que son partículas inhalables secadas por atomización.
8. Composición farmacéutica que comprende partículas inhalables de acuerdo con cualquiera de las reivindicaciones 1-7, donde las partículas están mezcladas con uno o más excipientes gruesos que presentan un tamaño de partícula medio de 15 a 250 μm .
9. Composición farmacéutica de acuerdo con la reivindicación 8, donde el

excipiente grueso es lactosa.

10. Composición farmacéutica de acuerdo con la reivindicación 9, donde el contenido de tiotropio base es de entre 0,02% y 0,8%.

11. Composición farmacéutica de acuerdo con cualquiera de las reivindicaciones 8-10, en forma de una cápsula para inhalación.

12. Composición farmacéutica de acuerdo con la reivindicación 11, donde la cápsula comprende hidroxipropilmetilcelulosa.

13. Procedimiento para preparar partículas inhalables de acuerdo con cualquiera de las reivindicaciones 1-7, que comprende las siguientes etapas:

- a) disolución o dispersión del agente estabilizante en un disolvente volátil miscible en agua que opcionalmente contiene agua para formar una solución o una suspensión;
- b) disolución de una sal de tiotropio, o un solvato de la misma, o cualquier forma sólida de la misma, en un disolvente volátil miscible en agua que opcionalmente contiene agua;
- c) mezclado de la solución de la etapa b) y la solución o suspensión de la etapa a).
- d) secado por atomización de la solución/ suspensión de la etapa c) para obtener las partículas deseadas.

14. Procedimiento para preparar la composición farmacéutica de acuerdo con cualquiera de las reivindicaciones 8-9, que comprende las etapas a) a d) definidas en la reivindicación 13, y que adicionalmente comprende la etapa de mezclado de partículas de la etapa d) con uno o más excipientes gruesos de un tamaño medio de partícula de 15 a 250 μm .

15. Procedimiento de acuerdo con cualquiera de las reivindicaciones 13-14, en el que cuando se forma una suspensión en la etapa a), el disolvente usado no contiene agua y el agente estabilizante está en forma de partículas de un tamaño medio de partícula de 1-9 μm .

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ANNEX 7

Microscopía electrónica de barrido (SEM)

Se obtuvieron imágenes de SEM de las siguientes muestras:

1. Muestra comparativa obtenida por un proceso de mezclado mecánico:
SPIRIVA.
2. Muestra obtenida por secado por atomización en forma de una matriz según la invención: **Tiotropium SD 702016.**
3. Mezcla de partículas secadas por atomización en forma de una matriz según la invención, y excipiente grueso: **12TIO12011CP02F1i.**

Las muestras anteriores se obtuvieron de la siguiente manera:

- La muestra comparativa (Spiriva) corresponde a una muestra del producto comercial SPIRIVA. De acuerdo con la información de prescripción del producto aprobada por la FDA y adjunta en el anexo 4, SPIRIVA contiene tiotropio mezclado (*blended*) con lactosa monohidrato (ver página 4, punto 11, segundo párrafo).
- La muestra secada por atomización (Tiotropium SD 702016) se obtuvo de una manera análoga al ejemplo 1 de la solicitud PCT/EP2009/062821, con la diferencia de que en este caso la solución se preparó por disolución de lactosa y tiotropio en agua en lugar de en una solución de etanol: agua.
- La muestra de mezcla (12TIO12011CP02F1i) que contiene partículas secadas por atomización y excipiente grueso se obtuvo mediante la mezcla de las partículas Tiotropium SD 702016 con el excipiente grueso (lactosa monohidrato D90 = 80,0 a 110,0 micras).

Las imágenes de SEM se obtuvieron mediante el uso de un HITACHI SU8000 Series UHR Cold-Emission FE-SEM. Las muestras se dispersaron en una película delgada de una resina epoxi de dos componentes y luego se recubrieron con una capa de platino.

Se obtuvieron las siguientes imágenes de SEM:

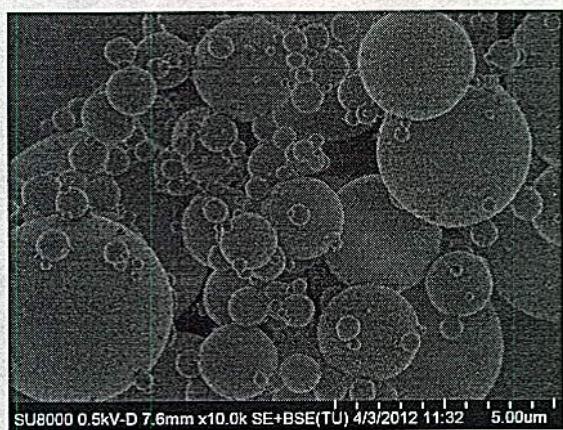
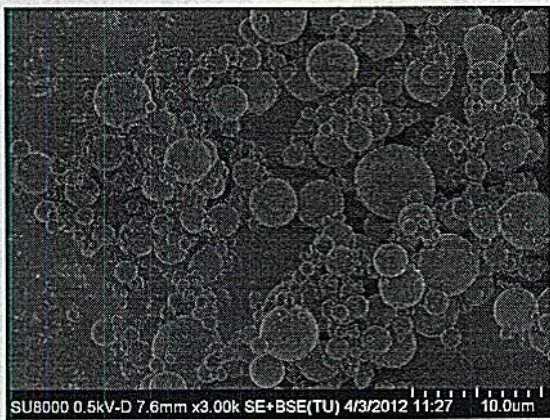
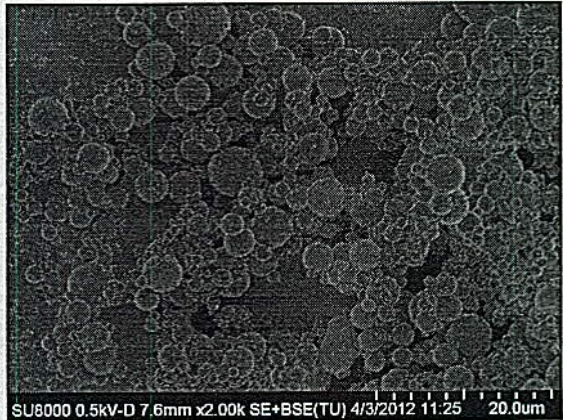
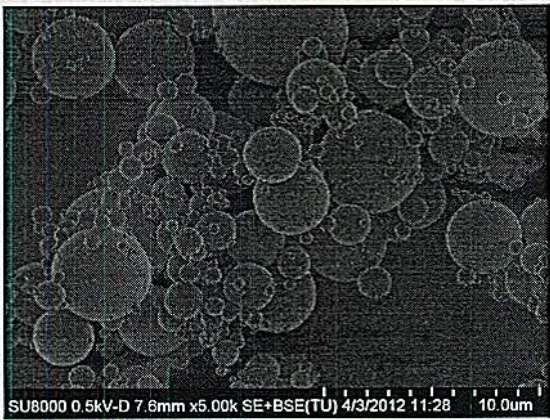
14

1. Imágenes de SEM de la muestra comparativa SPIRIVA a diferentes aumentos

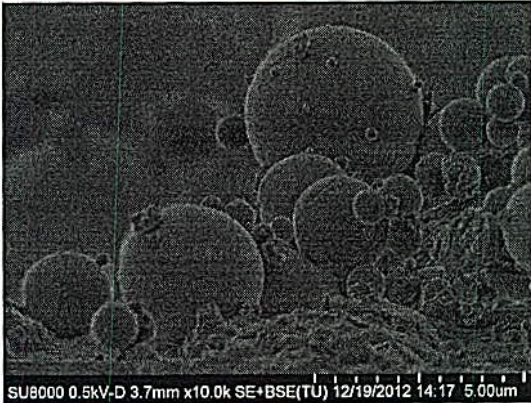
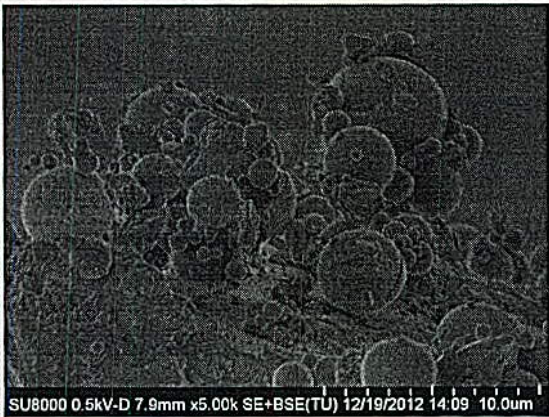


6

2. Imágenes de SEM de la muestra secada por atomización Tiotropium SD 702016 a diferentes aumentos



3. Imágenes de SEM de una mezcla de partículas secadas por atomización y excipiente grueso (12TIO12011CP02F1i) a diferentes aumentos



Resultados:

De acuerdo con las imágenes de SEM, en la muestra comparativa SPIRIVA se pueden ver las partículas más grandes con la forma típica de "tomahawk". Al enfocar en estas partículas, se observan partículas más finas con formas irregulares, siendo algunas de ellas partículas finas de lactosa y otras de tiotropio micronizado.

En contraste, la imágenes de SEM de las muestras según la invención (**Tiotropium SD 702016** y **12TIO12011CP02F1i**) muestran la forma esférica de las partículas. En la muestra de partículas secadas por atomización y excipiente grueso (**12TIO12011CP02F1i**), se puede observar, en primer lugar, la forma más típica "tomahawk" y, a continuación, cuando se enfoca en las imágenes, las partículas esféricas extendidas a lo largo de las partículas de lactosa.

En conclusión, la muestra comparativa y las muestras según la invención muestran claras diferencias estructurales. En particular:

- La muestra comparativa SPIRIVA se compone de lactosa gruesa y pequeñas partículas de forma irregular que contienen de lactosa y tiotropio micronizado, mientras que
- Las muestras secadas por atomización según la invención (**Tiotropium SD 702016** y **12TIO12011CP02F1i**) se componen de lactosa gruesa y pequeñas partículas esféricas que contienen una matriz en la que el tiotropio está dispersado molecularmente.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SPIRIVA HandiHaler safely and effectively. See full prescribing information for SPIRIVA HandiHaler.

SPIRIVA® HandiHaler® (tiotropium bromide inhalation powder)
Capsules for Respiratory Inhalation

DO NOT Swallow SPIRIVA Capsules
FOR ORAL INHALATION ONLY with the HandiHaler Device

Initial U.S. Approval: 2004

INDICATIONS AND USAGE

SPIRIVA HandiHaler is an anticholinergic indicated for the long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), and for reducing COPD exacerbations (1)

DOSAGE AND ADMINISTRATION

DO NOT swallow SPIRIVA capsules (2)
For Use with the HandiHaler Device ONLY (2)
For Oral Inhalation ONLY (2)

- Two inhalations of the powder contents of a single SPIRIVA capsule (18 mcg) once daily (2)

DOSAGE FORMS AND STRENGTHS

SPIRIVA capsules for oral inhalation: 18 mcg tiotropium powder, for use with HandiHaler device (3)

CONTRAINDICATIONS

- Hypersensitivity to ipratropium or tiotropium (4)

WARNINGS AND PRECAUTIONS

- Not for acute use: Not for use as a rescue medication (5.1)
- Immediate hypersensitivity reactions: Discontinue SPIRIVA HandiHaler at once and consider alternatives if immediate hypersensitivity reactions, including angioedema, occur. Use with caution in patients with severe hypersensitivity to milk proteins. (5.2)
- Paradoxical bronchospasm: Discontinue SPIRIVA HandiHaler and consider other treatments if paradoxical bronchospasm occurs (5.3)
- Worsening of narrow-angle glaucoma may occur. Use with caution in patients with narrow-angle glaucoma and instruct patients to consult a physician immediately if this occurs. (5.4)
- Worsening of urinary retention may occur. Use with caution in patients with prostatic hyperplasia or bladder-neck obstruction and instruct patients to consult a physician immediately if this occurs. (5.5)

ADVERSE REACTIONS

- The most common adverse reactions (>5% incidence in the 1-year placebo-controlled trials) were upper respiratory tract infection, dry mouth, sinusitis, pharyngitis, non-specific chest pain, urinary tract infection, dyspepsia, and rhinitis (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Boehringer Ingelheim Pharmaceuticals, Inc. at (800) 542-6257 or (800) 459-9906 TTY, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Anticholinergics: May interact additively with concomitantly used anticholinergic medications. Avoid administration of SPIRIVA HandiHaler with other anticholinergic-containing drugs. (7.2)

USE IN SPECIFIC POPULATIONS

Patients with moderate to severe renal impairment should be monitored closely for potential anticholinergic side effects (2, 8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 1/2011

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

SPIRIVA HandiHaler (tiotropium bromide inhalation powder) is indicated for the long-term, once-daily, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. SPIRIVA HandiHaler is indicated to reduce exacerbations in COPD patients.

2 DOSAGE AND ADMINISTRATION

DO NOT SWALLOW SPIRIVA CAPSULES

FOR USE WITH HANDIHALER DEVICE ONLY

FOR ORAL INHALATION ONLY

SPIRIVA capsules must not be swallowed as the intended effects on the lungs will not be obtained. The contents of the SPIRIVA capsules are only for oral inhalation and should only be used with the HandiHaler device [see Overdosage (10)].

The recommended dose of SPIRIVA HandiHaler is two inhalations of the powder contents of one SPIRIVA capsule, once-daily, with the HandiHaler device [see Patient Counseling Information (17)].

For administration of SPIRIVA HandiHaler, a SPIRIVA capsule is placed into the center chamber of the HandiHaler device. The SPIRIVA capsule is pierced by pressing and releasing the green piercing button on the side of the HandiHaler device. The tiotropium formulation is dispersed into the air stream when the patient inhales through the mouthpiece [see Patient Counseling Information (17)].

No dosage adjustment is required for geriatric, hepatically-impaired, or renally-impaired patients. However, patients with moderate to severe renal impairment given SPIRIVA HandiHaler should be monitored closely for anticholinergic effects [see Warnings and Precautions (5.6), Use in Specific Populations (8.5, 8.6, 8.7), and Clinical Pharmacology (12.3)].

3 DOSAGE FORMS AND STRENGTHS

SPIRIVA HandiHaler consists of SPIRIVA capsules and a HandiHaler device. SPIRIVA capsules contain 18 mcg dry powder formulation of tiotropium in a light green, hard gelatin capsule with TI 01 printed on one side and Boehringer Ingelheim company logo on the other side.

4 CONTRAINDICATIONS

SPIRIVA HandiHaler is contraindicated in patients with a hypersensitivity to ipratropium or tiotropium. In clinical trials and postmarketing experience with SPIRIVA HandiHaler, immediate hypersensitivity reactions, including angioedema (including swelling of the lips, tongue, or throat), itching, or rash have been reported.

5 WARNINGS AND PRECAUTIONS

5.1 Not for Acute Use

SPIRIVA HandiHaler is intended as a once-daily maintenance treatment for COPD and is not indicated for the initial treatment of acute episodes of bronchospasm (i.e., rescue therapy).

5.2 Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions, including angioedema (including swelling of the lips, tongue, or throat), itching, or rash may occur after administration of SPIRIVA HandiHaler. If such a reaction occurs, therapy with SPIRIVA HandiHaler should be stopped at once and alternative treatments should be considered. Given the similar structural formula of atropine to tiotropium, patients with a history of hypersensitivity reactions to atropine should be closely monitored for similar hypersensitivity reactions to SPIRIVA HandiHaler. In addition, SPIRIVA HandiHaler should be used with caution in patients with severe hypersensitivity to milk proteins.

5.3 Paradoxical Bronchospasm

Inhaled medicines, including SPIRIVA HandiHaler, may cause paradoxical bronchospasm. If this occurs, treatment with SPIRIVA HandiHaler should be stopped and other treatments considered.

5.4 Worsening of Narrow-Angle Glaucoma

SPIRIVA HandiHaler should be used with caution in patients with narrow-angle glaucoma. Prescribers and patients should be alert for signs and symptoms of acute narrow-angle glaucoma (e.g., eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema). Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

5.5 Worsening of Urinary Retention

SPIRIVA HandiHaler should be used with caution in patients with urinary retention. Prescribers and patients should be alert for signs and symptoms of prostatic hyperplasia or bladder-neck obstruction (e.g., difficulty passing urine, painful urination). Instruct patients to consult a physician immediately should any of these signs or symptoms develop.

5.6 Renal Impairment

As a predominantly renally excreted drug, patients with moderate to severe renal impairment (creatinine clearance of ≤50 mL/min) treated with SPIRIVA HandiHaler should be monitored closely for anticholinergic side effects [see Clinical Pharmacology (12.3)].

6 ADVERSE REACTIONS

The following adverse reactions are described, or described in greater detail, in other sections:

- Immediate hypersensitivity reactions [see Warnings and Precautions (5.2)]
- Paradoxical bronchospasm [see Warnings and Precautions (5.3)]
- Worsening of narrow-angle glaucoma [see Warnings and Precautions (5.4)]
- Worsening of urinary retention [see Warnings and Precautions (5.5)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6-Month to 1-Year Trials

The data described below reflect exposure to SPIRIVA HandiHaler in 2663 patients. SPIRIVA HandiHaler was studied in two 1-year placebo-controlled trials, two 1-year active-controlled trials, and two 6-month placebo-controlled trials in patients with COPD. In these trials, 1308 patients were treated with SPIRIVA HandiHaler at the recommended dose of 18 mcg once a day. The population had an age ranging from 39 to 87 years with 65% to 85% males, 95% Caucasian, and had COPD with a mean pre-bronchodilator forced expiratory volume in one second (FEV₁) percent predicted of 39% to 43%. Patients with narrow-angle glaucoma, or symptomatic prostatic hypertrophy or bladder outlet obstruction were excluded from these trials. An additional 6-month trial conducted in a Veteran's Affairs setting is not included

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in this safety database because only serious adverse events were collected.

The most commonly reported adverse drug reaction was dry mouth. Dry mouth was usually mild and often resolved during continued treatment. Other reactions reported in individual patients and consistent with possible anticholinergic effects included constipation, tachycardia, blurred vision, glaucoma (new onset or worsening), dysuria, and urinary retention.

Four multicenter, 1-year, placebo-controlled and active-controlled trials evaluated SPIRIVA HandiHaler in patients with COPD. Table 1 shows all adverse reactions that occurred with a frequency of $\geq 3\%$ in the SPIRIVA HandiHaler group in the 1-year placebo-controlled trials where the rates in the SPIRIVA HandiHaler group exceeded placebo by $\geq 1\%$. The frequency of corresponding reactions in the ipratropium-controlled trials is included for comparison.

Table 1 Adverse Reactions (% Patients) in One-Year COPD Clinical Trials

Body System (Event)	Placebo-Controlled Trials		Ipratropium-Controlled Trials	
	SPIRIVA (n = 550)	Placebo (n = 371)	SPIRIVA (n = 356)	Ipratropium (n = 179)
Body as a Whole				
Chest Pain (non-specific)	7	5	5	2
Edema, Dependent	5	4	3	5
Gastrointestinal System Disorders				
Dry Mouth	16	3	12	6
Dyspepsia	6	5	1	1
Abdominal Pain	5	3	6	6
Constipation	4	2	1	1
Vomiting	4	2	1	2
Musculoskeletal System				
Myalgia	4	3	4	3
Resistance Mechanism Disorders				
Infection	4	3	1	3
Moniliasis	4	2	3	2
Respiratory System (Upper)				
Upper Respiratory Tract Infection	41	37	43	35
Sinusitis	11	9	3	2
Pharyngitis	9	7	7	3
Rhinitis	6	5	3	2
Epistaxis	4	2	1	1
Skin and Appendage Disorders				
Rash	4	2	2	2
Urinary System				
Urinary Tract Infection	7	5	4	2

Arthritis, coughing, and influenza-like symptoms occurred at a rate of $\geq 3\%$ in the SPIRIVA HandiHaler treatment group, but were $<1\%$ in excess of the placebo group.

Other reactions that occurred in the SPIRIVA HandiHaler group at a frequency of 1% to 3% in the placebo-controlled trials where the rates exceeded that in the placebo group include: *Body as a Whole*: allergic reaction, leg pain; *Central and Peripheral Nervous System*: dysphonia, paresthesia; *Gastrointestinal System Disorders*: gastrointestinal disorder not otherwise specified (NOS), gastroesophageal reflux, stomatitis (including ulcerative stomatitis); *Metabolic and Nutritional Disorders*: hypercholesterolemia, hyperglycemia; *Musculoskeletal System Disorders*: skeletal pain; *Cardiac Events*: angina pectoris (including aggravated angina pectoris); *Psychiatric Disorder*: depression; *Infections*: herpes zoster; *Respiratory System Disorder (Upper)*: laryngitis; *Vision Disorder*: cataract. In addition, among the adverse reactions observed in the clinical trials with an incidence of $<1\%$ were atrial fibrillation, supraventricular tachycardia, angioedema, and urinary retention.

In the 1-year trials, the incidence of dry mouth, constipation, and urinary tract infection increased with age [see *Use in Specific Populations* (8.5)].

Two multicenter, 6-month, controlled studies evaluated SPIRIVA HandiHaler in patients with COPD. The adverse reactions and the incidence rates were similar to those seen in the 1-year controlled trials.

4-Year Trial

The data described below reflect exposure to SPIRIVA HandiHaler in 5992 COPD patients in a 4-year placebo-controlled trial. In this trial, 2986 patients were treated with SPIRIVA HandiHaler at the recommended dose of 18 mcg once a day. The population had an age range from 40 to 88 years, was 75% male, 90% Caucasian, and had COPD with a mean pre-bronchodilator FEV₁ percent predicted of 40%. Patients with narrow-angle glaucoma, or symptomatic prostatic hypertrophy or bladder outlet obstruction were excluded from these trials. When the adverse reactions were analyzed with a frequency of $\geq 3\%$ in the SPIRIVA HandiHaler group where the rates in the SPIRIVA HandiHaler group exceeded placebo by $\geq 1\%$, adverse reactions included (SPIRIVA HandiHaler, placebo): pharyngitis (12.5%, 10.8%), sinusitis (6.5%, 5.3%), headache (5.7%, 4.5%), constipation (5.1%, 3.7%), dry mouth (5.1%, 2.7%), depression (4.4%, 3.3%), insomnia (4.4%, 3.0%), and arthralgia (4.2%, 3.1%).

Additional Adverse Reactions

Other adverse reactions not previously listed that were reported more frequently in COPD patients treated with SPIRIVA HandiHaler than placebo include: dehydration, skin ulcer, stomatitis, gingivitis, oropharyngeal candidiasis, dry skin, skin infection, and joint swelling.

6.2 Postmarketing Experience

Adverse reactions have been identified during worldwide post-approval use of SPIRIVA HandiHaler. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These adverse reactions are: application site irritation (glossitis, mouth ulceration, and pharyngolaryngeal pain), dizziness, dysphagia, hoarseness, intestinal obstruction including ileus paralytic, intraocular pressure increased, oral candidiasis, palpitations, pruritus, tachycardia, throat irritation, and urticaria.

7 DRUG INTERACTIONS

7.1 Sympathomimetics, Methylxanthines, Steroids

SPIRIVA HandiHaler has been used concomitantly with short-acting and long-acting sympathomimetic (beta-agonists) bronchodilators, methylxanthines, and oral and

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inhaled steroids without increases in adverse drug reactions.

7.2 Anticholinergics

There is potential for an additive interaction with concomitantly used anticholinergic medications. Therefore, avoid coadministration of SPIRIVA HandiHaler with other anticholinergic-containing drugs as this may lead to an increase in anticholinergic adverse effects [see *Warnings and Precautions (5.4, 5.5) and Adverse Reactions (6)*].

7.3 Cimetidine, Ranitidine

No clinically significant interaction occurred between tiotropium and cimetidine or ranitidine [see *Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects, Pregnancy Category C.

There are no adequate and well-controlled studies in pregnant women. SPIRIVA HandiHaler should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

No evidence of structural alterations was observed in rats and rabbits at inhalation tiotropium doses of up to approximately 660 and 6 times the recommended human daily inhalation dose (RHDID) on a mg/m² basis, respectively. However, in rats, tiotropium caused fetal resorption, litter loss, decreases in the number of live pups at birth and the mean pup weights, and a delay in pup sexual maturation at inhalation tiotropium doses of approximately 35 times the RHDID on a mg/m² basis. In rabbits, tiotropium caused an increase in post-implantation loss at an inhalation dose of approximately 360 times the RHDID on a mg/m² basis. Such effects were not observed at inhalation doses of approximately 4 and 80 times the RHDID on a mg/m² basis, respectively. These dose multiples may be over-estimated due to difficulties in measuring deposited doses in animal inhalation studies.

8.2 Labor and Delivery

The safety and effectiveness of SPIRIVA HandiHaler has not been studied during labor and delivery.

8.3 Nursing Mothers

Clinical data from nursing women exposed to tiotropium are not available. Based on lactating rodent studies, tiotropium is excreted into breast milk. It is not known whether tiotropium is excreted in human milk, but because many drugs are excreted in human milk and given these findings in rats, caution should be exercised if SPIRIVA HandiHaler is administered to a nursing woman.

8.4 Pediatric Use

SPIRIVA HandiHaler is approved for use in the maintenance treatment of bronchospasm associated with COPD and for the reduction of COPD exacerbations. COPD does not normally occur in children. The safety and effectiveness of SPIRIVA HandiHaler in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of patients who received SPIRIVA HandiHaler in the 1-year clinical trials, 426 were <65 years, 375 were 65 to 74 years, and 105 were ≥75 years of age. Within each age subgroup, there were no differences between the proportion of patients with adverse events in the SPIRIVA HandiHaler and the comparator groups for most events. Dry mouth increased with age in the SPIRIVA HandiHaler group (differences from placebo were 9.0%, 17.1%, and 16.2% in the aforementioned age subgroups). A higher frequency of constipation and urinary tract infections with increasing age was observed in the SPIRIVA HandiHaler group in the placebo-controlled studies. The differences from placebo for constipation were 0%, 1.8%, and 7.8% for each of the age groups. The differences from placebo for urinary tract infections were -0.6%, 4.6%, and 4.5%. No overall differences in effectiveness were observed among these groups. Based on available data, no adjustment of SPIRIVA HandiHaler dosage in geriatric patients is warranted [see *Clinical Pharmacology (12.3)*].

8.6 Renal Impairment

Patients with moderate to severe renal impairment (creatinine clearance of ≤50 mL/min) treated with SPIRIVA HandiHaler should be monitored closely for anticholinergic side effects [see *Dosage and Administration (2)*, *Warnings and Precautions (5.4)*, and *Clinical Pharmacology (12.3)*].

8.7 Hepatic Impairment

The effects of hepatic impairment on the pharmacokinetics of tiotropium were not studied.

10 OVERDOSAGE

High doses of tiotropium may lead to anticholinergic signs and symptoms. However, there were no systemic anticholinergic adverse effects following a single inhaled dose of up to 282 mcg tiotropium in 6 healthy volunteers. In a study of 12 healthy volunteers, bilateral conjunctivitis and dry mouth were seen following repeated once-daily inhalation of 141 mcg of tiotropium.

Accidental Ingestion

Acute intoxication by inadvertent oral ingestion of SPIRIVA capsules is unlikely since it is not well-absorbed systemically.

A case of overdose has been reported from postmarketing experience. A female patient was reported to have inhaled 30 capsules over a 2.5 day period, and developed altered mental status, tremors, abdominal pain, and severe constipation. The patient was hospitalized, SPIRIVA HandiHaler was discontinued, and the constipation was treated with an enema. The patient recovered and was discharged on the same day.

No mortality was observed at inhalation tiotropium doses up to 32.4 mg/kg in mice, 267.7 mg/kg in rats, and 0.6 mg/kg in dogs. These doses correspond to 7300, 120,000, and 850 times the recommended human daily inhalation dose on a mg/m² basis, respectively. These dose multiples may be over-estimated due to difficulties in measuring deposited doses in animal inhalation studies.

11 DESCRIPTION

SPIRIVA HandiHaler consists of a capsule dosage form containing a dry powder formulation of tiotropium intended for oral inhalation only with the HandiHaler device.

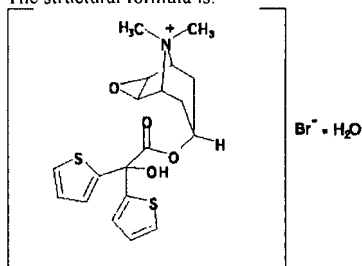
Each light green, hard gelatin SPIRIVA capsule contains 18 mcg tiotropium (equivalent to 22.5 mcg tiotropium bromide monohydrate) blended with lactose monohydrate (which may contain milk proteins) as the carrier.

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The dry powder formulation within the SPIRIVA capsule is intended for oral inhalation only.

The active component of SPIRIVA HandiHaler is tiotropium. The drug substance, tiotropium bromide monohydrate, is an anticholinergic with specificity for muscarinic receptors. It is chemically described as (1 α , 2 β , 4 β , 5 α , 7 β)-7-[(Hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.0^{2,4}]nonane bromide monohydrate. It is a synthetic, non-chiral, quaternary ammonium compound. Tiotropium bromide is a white or yellowish white powder. It is sparingly soluble in water and soluble in methanol.

The structural formula is:



Tiotropium bromide (monohydrate) has a molecular mass of 490.4 and a molecular formula of C₁₉H₂₂NO₄S₂Br • H₂O.

The HandiHaler device is an inhalation device used to inhale the dry powder contained in the SPIRIVA capsule. The dry powder is delivered from the HandiHaler device at flow rates as low as 20 L/min. Under standardized *in vitro* testing, the HandiHaler device delivers a mean of 10.4 mcg tiotropium when tested at a flow rate of 39 L/min for 3.1 seconds (2 L total). In a study of 26 adult patients with COPD and severely compromised lung function [mean FEV₁ 1.02 L (range 0.45 to 2.24 L); 37.6% of predicted (range 16% to 65%)], the median peak inspiratory flow (PIF) through the HandiHaler device was 30.0 L/min (range 20.4 to 45.6 L/min). The amount of drug delivered to the lungs will vary depending on patient factors such as inspiratory flow and peak inspiratory flow through the HandiHaler device, which may vary from patient to patient, and may vary with the exposure time of the SPIRIVA capsule outside the blister pack.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tiotropium is a long-acting, antimuscarinic agent, which is often referred to as an anticholinergic. It has similar affinity to the subtypes of muscarinic receptors, M₁ to M₅. In the airways, it exhibits pharmacological effects through inhibition of M₃-receptors at the smooth muscle leading to bronchodilation. The competitive and reversible nature of antagonism was shown with human and animal origin receptors and isolated organ preparations. In preclinical *in vitro* as well as *in vivo* studies, prevention of methacholine-induced bronchoconstriction effects was dose-dependent and lasted longer than 24 hours. The bronchodilation following inhalation of tiotropium is predominantly a site-specific effect.

12.2 Pharmacodynamics

Cardiovascular Effects

In a multicenter, randomized, double-blind trial that enrolled 198 patients with COPD, the number of subjects with changes from baseline-corrected QT interval of 30 to 60 msec was higher in the SPIRIVA HandiHaler group as compared with placebo. This difference was apparent using both the Bazett (QTcB) [20 (20%) patients vs 12 (12%) patients] and Fredericia (QTcF) [16 (16%) patients vs 1 (1%) patient] corrections of QT for heart rate. No patients in either group had either QTcB or QTcF of >500 msec. Other clinical studies with SPIRIVA HandiHaler did not detect an effect of the drug on QTc intervals.

The effect of SPIRIVA HandiHaler on QT interval was also evaluated in a randomized, placebo- and positive-controlled crossover study in 53 healthy volunteers. Subjects received SPIRIVA HandiHaler 18 mcg, 54 mcg (3 times the recommended dose), or placebo for 12 days. ECG assessments were performed at baseline and throughout the dosing interval following the first and last dose of study medication. Relative to placebo, the maximum mean change from baseline in study-specific QTc interval was 3.2 msec and 0.8 msec for SPIRIVA HandiHaler 18 mcg and 54 mcg, respectively. No subject showed a new onset of QTc >500 msec or QTc changes from baseline of ≥ 60 msec.

12.3 Pharmacokinetics

Tiotropium is administered by dry powder inhalation. In common with other inhaled drugs, the majority of the delivered dose is deposited in the gastrointestinal tract and, to a lesser extent, in the lung, the intended organ. Many of the pharmacokinetic data described below were obtained with higher doses than recommended for therapy.

Absorption

Following dry powder inhalation by young healthy volunteers, the absolute bioavailability of 19.5% suggests that the fraction reaching the lung is highly bioavailable. It is expected from the chemical structure of the compound (quaternary ammonium compound) that tiotropium is poorly absorbed from the gastrointestinal tract. The effect of food on tiotropium's bioavailability has not been studied. Oral solutions of tiotropium have an absolute bioavailability of 2% to 3%. Maximum tiotropium plasma concentrations were observed 5 minutes after inhalation.

Distribution

Tiotropium shows a volume of distribution of 32 L/kg indicating that the drug binds extensively to tissues. The human plasma protein binding for tiotropium is 72%. At steady state, peak tiotropium plasma levels in COPD patients were 17 to 19 pg/mL when measured 5 minutes after dry powder inhalation of an 18 mcg dose and decreased in a multi-compartmental manner. Steady-state trough plasma concentrations were 3 to 4 pg/mL. Local concentrations in the lung are not known, but the mode of administration suggests substantially higher concentrations in the lung. Studies in rats have shown that tiotropium does not readily penetrate the blood-brain barrier.

Metabolism

The extent of metabolism appears to be small. This is evident from a urinary excretion of 74% of unchanged substance after an intravenous dose to young healthy volunteers. Tiotropium, an ester, is nonenzymatically cleaved to the alcohol *N*-methylscopine and dithienylglycolic acid, neither of which binds to muscarinic receptors.

In vitro experiments with human liver microsomes and human hepatocytes suggest that a fraction of the administered dose (74% of an intravenous dose is excreted unchanged in the urine, leaving 25% for metabolism) is metabolized by cytochrome P450-dependent oxidation and subsequent glutathione conjugation to a variety of Phase II metabolites. This enzymatic pathway can be inhibited by CYP450 2D6 and 3A4 inhibitors, such as quinidine, ketoconazole, and gestodene. Thus, CYP450 2D6 and 3A4 are involved in the metabolic pathway that is responsible for the elimination of a small part of the administered dose. *In vitro* studies using human liver

microsomes showed that tiotropium in supra-therapeutic concentrations did not inhibit CYP450 1A1, 1A2, 2B6, 2C9, 2C19, 2D6, 2E1, or 3A4.

Elimination

The terminal elimination half-life of tiotropium was between 5 and 6 days following inhalation. Total clearance was 880 mL/min after an intravenous dose in young healthy volunteers with an inter-individual variability of 22%. Intravenously administered tiotropium was mainly excreted unchanged in urine (74%). After dry powder inhalation, urinary excretion was 14% of the dose, the remainder being mainly non-absorbed drug in the gut which was eliminated via the feces. The renal clearance of tiotropium exceeds the creatinine clearance, indicating active secretion into the urine. After chronic once-daily inhalation by COPD patients, pharmacokinetic steady state was reached after 2 to 3 weeks with no accumulation thereafter.

Drug Interactions

An interaction study with tiotropium (14.4 mcg intravenous infusion over 15 minutes) and cimetidine 400 mg three times daily or ranitidine 300 mg once daily was conducted. Concomitant administration of cimetidine with tiotropium resulted in a 20% increase in the AUC_{0-4h} , a 28% decrease in the renal clearance of tiotropium and no significant change in the C_{max} and amount excreted in urine over 96 hours. Co-administration of tiotropium with ranitidine did not affect the pharmacokinetics of tiotropium.

Specific Populations

Geriatric Patients

As expected for drugs predominantly excreted renally, advanced age was associated with a decrease of tiotropium renal clearance (326 mL/min in COPD patients <58 years to 163 mL/min in COPD patients >70 years), which may be explained by decreased renal function. Tiotropium excretion in urine after inhalation decreased from 14% (young healthy volunteers) to about 7% (COPD patients). Plasma concentrations were numerically increased with advancing age within COPD patients (43% increase in AUC_{0-4} after dry powder inhalation), which was not significant when considered in relation to inter- and intra-individual variability [see *Dosage and Administration (2) and Use in Specific Populations (8.5)*].

Renal Impairment

Since tiotropium is predominantly renally excreted, renal impairment was associated with increased plasma drug concentrations and reduced drug clearance after both intravenous infusion and dry powder inhalation. Mild renal impairment (creatinine clearance of 50 to 80 mL/min), which is often seen in elderly patients, increased tiotropium plasma concentrations (39% increase in AUC_{0-4} after intravenous infusion). In COPD patients with moderate to severe renal impairment (creatinine clearance of <50 mL/min), the intravenous administration of tiotropium resulted in doubling of the plasma concentrations (82% increase in AUC_{0-4}), which was confirmed by plasma concentrations after dry powder inhalation. Patients with moderate to severe renal impairment (creatinine clearance of ≤50 mL/min) treated with SPIRIVA HandiHaler should be monitored closely for anticholinergic side effects [see *Dosage and Administration (2), Warnings and Precautions (5.4), and Use in Specific Populations (8.6)*].

Hepatic Impairment

The effects of hepatic impairment on the pharmacokinetics of tiotropium were not studied.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No evidence of tumorigenicity was observed in a 104-week inhalation study in rats at tiotropium doses up to 0.059 mg/kg/day, in an 83-week inhalation study in female mice at doses up to 0.145 mg/kg/day, and in a 101-week inhalation study in male mice at doses up to 0.002 mg/kg/day. These doses correspond to approximately 25, 35, and 0.5 times the recommended human daily inhalation dose (RHDID) on a mg/m² basis, respectively. These dose multiples may be over-estimated due to difficulties in measuring deposited doses in animal inhalation studies.

Tiotropium bromide demonstrated no evidence of mutagenicity or clastogenicity in the following assays: the bacterial gene mutation assay, the V79 Chinese hamster cell mutagenesis assay, the chromosomal aberration assays in human lymphocytes *in vitro* and mouse micronucleus formation *in vivo*, and the unscheduled DNA synthesis in primary rat hepatocytes *in vitro* assay.

In rats, decreases in the number of corpora lutea and the percentage of implants were noted at inhalation tiotropium doses of 0.078 mg/kg/day or greater (approximately 35 times the RHDID on a mg/m² basis). No such effects were observed at 0.009 mg/kg/day (approximately 4 times than the RHDID on a mg/m² basis). The fertility index, however, was not affected at inhalation doses up to 1.689 mg/kg/day (approximately 760 times the RHDID on a mg/m² basis). These dose multiples may be over-estimated due to difficulties in measuring deposited doses in animal inhalation studies.

13.2 Animal Toxicology and Pharmacology

Reproductive Toxicology Studies

No evidence of fetal structural alteration was observed in rats and rabbits at inhalation tiotropium doses of up to 1.471 and 0.007 mg/kg/day, respectively. These doses correspond to approximately 660 and 6 times the RHDID on a mg/m² basis, respectively. However, in rats, fetal resorption, litter loss, decreases in the number of live pups at birth and the mean pup weights, and a delay in pup sexual maturation were observed at inhalation tiotropium doses of ≥0.078 mg/kg (approximately 35 times the RHDID on a mg/m² basis). In rabbits, an increase in post-implantation loss was observed at an inhalation dose of 0.4 mg/kg/day (approximately 360 times the RHDID on a mg/m² basis). Such effects were not observed at inhalation doses of 0.009 and up to 0.088 mg/kg/day in rats and rabbits, respectively. These doses correspond to approximately 4 and 80 times the RHDID on a mg/m² basis, respectively. These dose multiples may be over-estimated due to difficulties in measuring deposited doses in animal inhalation studies.

14 CLINICAL STUDIES

The SPIRIVA HandiHaler (tiotropium bromide inhalation powder) clinical development program consisted of six Phase 3 studies in 2663 patients with COPD (1308 receiving SPIRIVA HandiHaler): two 1-year, placebo-controlled studies, two 6-month, placebo-controlled studies and two 1-year, ipratropium-controlled studies. These studies enrolled patients who had a clinical diagnosis of COPD, were 40 years of age or older, had a history of smoking greater than 10 pack-years, had a forced expiratory volume in one second (FEV₁) less than or equal to 60% or 65% of predicted, and a ratio of FEV₁/FVC of less than or equal to 0.7.

In these studies, SPIRIVA HandiHaler, administered once-daily in the morning, provided improvement in lung function (FEV₁), with peak effect occurring within 3 hours following the first dose.

Two additional trials evaluated exacerbations: a 6-month, randomized, double-blind, placebo-controlled, multicenter clinical trial of 1829 COPD patients in a US Veterans Affairs setting and a 4-year, randomized, double-blind, placebo-controlled, multicenter, clinical trial of 5992 COPD patients. Long-term effects on lung function and other outcomes were also evaluated in the 4-year multicenter trial.

6-Month to 1-Year Effects on Lung Function

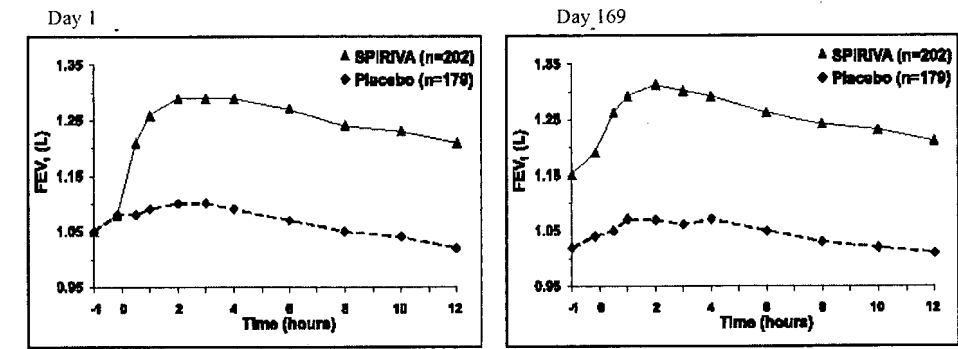
In the 1-year, placebo-controlled trials, the mean improvement in FEV₁ at 30 minutes was 0.13 liters (13%) with a peak improvement of 0.24 liters (24%) relative to

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baseline after the first dose (Day 1). Further improvements in FEV₁ and forced vital capacity (FVC) were observed with pharmacodynamic steady state reached by Day 8 with once-daily treatment. The mean peak improvement in FEV₁, relative to baseline, was 0.28 to 0.31 liters (28% to 31%), after 1 week (Day 8) of once-daily treatment. Improvement of lung function was maintained for 24 hours after a single dose and consistently maintained over the 1-year treatment period with no evidence of tolerance.

In the two 6-month, placebo-controlled trials, serial spirometric evaluations were performed throughout daytime hours in Trial A (12 hours) and limited to 3 hours in Trial B. The serial FEV₁ values over 12 hours (Trial A) are displayed in Figure 1. These trials further support the improvement in pulmonary function (FEV₁) with SPIRIVA HandiHaler, which persisted over the spirometric observational period. Effectiveness was maintained for 24 hours after administration over the 6-month treatment period.

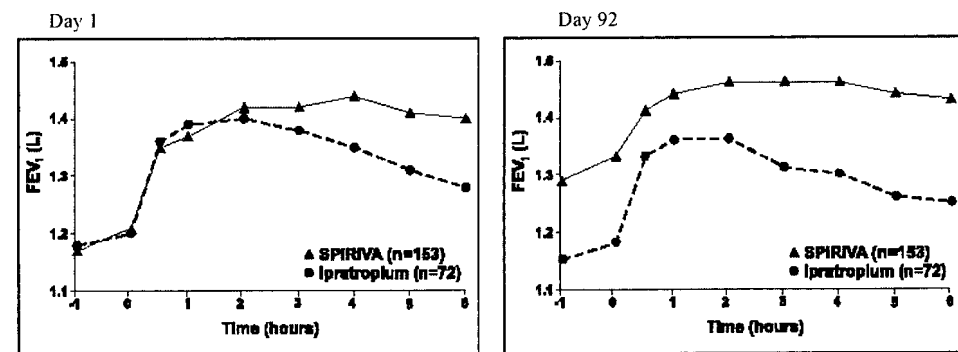
Figure 1 Mean FEV₁ Over Time (prior to and after administration of study drug) on Days 1 and 169 for Trial A (a Six-Month Placebo-Controlled Study)*



*Means adjusted for center, treatment, and baseline effect. On Day 169, a total of 183 and 149 patients in the SPIRIVA HandiHaler and placebo groups, respectively, completed the trial. The data for the remaining patients were imputed using the last observation or least favorable observation carried forward.

Results of each of the 1-year ipratropium-controlled trials were similar to the results of the 1-year placebo-controlled trials. The results of one of these trials are shown in Figure 2.

Figure 2 Mean FEV₁ Over Time (0 to 6 hours post-dose) on Days 1 and 92, Respectively for One of the Two Ipratropium-Controlled Studies*



*Means adjusted for center, treatment, and baseline effect. On Day 92 (primary endpoint), a total of 151 and 69 patients in the SPIRIVA HandiHaler and ipratropium groups, respectively, completed through 3 months of observation. The data for the remaining patients were imputed using the last observation or least favorable observation carried forward.

A randomized, placebo-controlled clinical study in 105 patients with COPD demonstrated that bronchodilation was maintained throughout the 24-hour dosing interval in comparison to placebo, regardless of whether SPIRIVA HandiHaler was administered in the morning or in the evening.

Throughout each week of the one-year treatment period in the two placebo-controlled trials, patients taking SPIRIVA HandiHaler had a reduced requirement for the use of rescue short-acting beta₂-agonists. Reduction in the use of rescue short-acting beta₂-agonists, as compared to placebo, was demonstrated in one of the two 6-month studies.

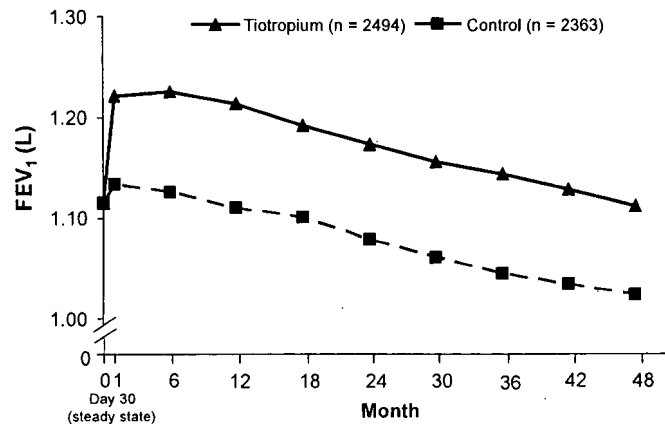
4-Year Effects on Lung Function

A 4-year, randomized, double-blind, placebo-controlled, multicenter clinical trial involving 5992 COPD patients was conducted to evaluate the long-term effects of SPIRIVA HandiHaler on disease progression (rate of decline in FEV₁). Patients were permitted to use all respiratory medications (including short-acting and long-acting beta-agonists, inhaled and systemic steroids, and theophyllines) other than inhaled anticholinergics. The patients were 40 to 88 years of age, 75% male, and 90% Caucasian with a diagnosis of COPD and a mean pre-bronchodilator FEV₁ of 39% predicted (range = 9% to 76%) at study entry. There was no difference between the groups in either of the co-primary efficacy endpoints, yearly rate of decline in pre- and post-bronchodilator FEV₁, as demonstrated by similar slopes of FEV₁ decline over time (Figure 3).

SPIRIVA HandiHaler maintained improvements in trough (pre-dose) FEV₁ (adjusted means over time: 87 to 103 mL) throughout the 4 years of the study (Figure 3).

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Figure 3 Trough (pre-dose) FEV₁ Mean Values at Each Time Point



Repeated measure ANOVA was used to estimate means. Means are adjusted for baseline measurements. Baseline trough FEV₁ (observed mean) = 1.12. Patients with ≥ 3 acceptable pulmonary function tests after Day 30 and non-missing baseline value were included in the analysis.

Exacerbations

The effect of SPIRIVA HandiHaler on COPD exacerbations was evaluated in two clinical trials: a 4-year clinical trial described above and a 6-month clinical trial of 1829 COPD patients in a Veterans Affairs setting. In the 6-month trial, COPD exacerbations were defined as a complex of respiratory symptoms (increase or new onset) of more than one of the following: cough, sputum, wheezing, dyspnea, or chest tightness with a duration of at least 3 days requiring treatment with antibiotics, systemic steroids, or hospitalization. The population had an age ranging from 40 to 90 years with 99% males, 91% Caucasian, and had COPD with a mean pre-bronchodilator FEV₁ percent predicted of 36% (range = 8% to 93%). Patients were permitted to use respiratory medications (including short-acting and long-acting beta-agonists, inhaled and systemic steroids, and theophyllines) other than inhaled anticholinergics. In the 6-month trial, the co-primary endpoints were the proportion of patients with COPD exacerbation and the proportion of patients with hospitalization due to COPD exacerbation. SPIRIVA HandiHaler significantly reduced the proportion of COPD patients who experienced exacerbations compared to placebo (27.9% vs 32.3%, respectively; Odds Ratio (OR) (tiotropium/placebo) = 0.81; 95% CI = 0.66, 0.99; p = 0.037). The proportion of patients with hospitalization due to COPD exacerbations in patients who used SPIRIVA HandiHaler compared to placebo was 7.0% vs 9.5%, respectively; OR = 0.72; 95% CI = 0.51, 1.01; p = 0.056.

Exacerbations were evaluated as a secondary outcome in the 4-year multicenter trial. In this trial, COPD exacerbations were defined as an increase or new onset of more than one of the following respiratory symptoms (cough, sputum, sputum purulence, wheezing, dyspnea) with a duration of three or more days requiring treatment with antibiotics and/or systemic (oral, intramuscular, or intravenous) steroids. SPIRIVA HandiHaler significantly reduced the risk of an exacerbation by 14% (Hazard Ratio (HR) = 0.86; 95% CI = 0.81, 0.91; p < 0.001) and reduced the risk of exacerbation-related hospitalization by 14% (HR = 0.86; 95% CI = 0.78, 0.95; p < 0.002) compared to placebo. The median time to first exacerbation was delayed from 12.5 months (95% CI = 11.5, 13.8) in the placebo group to 16.7 months (95% CI = 14.9, 17.9) in the SPIRIVA HandiHaler group.

16 HOW SUPPLIED/STORAGE AND HANDLING

SPIRIVA HandiHaler consists of SPIRIVA capsules and the HandiHaler device. SPIRIVA capsules contain 18 mcg of tiotropium and are light green, with the Boehringer Ingelheim company logo on the SPIRIVA capsule cap and TI 01 on the SPIRIVA capsule body, or vice versa.

The HandiHaler device is gray colored with a green piercing button. It is imprinted with SPIRIVA HandiHaler (tiotropium bromide inhalation powder), the Boehringer Ingelheim company logo, and the Pfizer company logo. It is also imprinted to indicate that SPIRIVA capsules should not be stored in the HandiHaler device and that the HandiHaler device is only to be used with SPIRIVA capsules.

SPIRIVA capsules are packaged in an aluminum/aluminum blister card and joined along a perforated-cut line. SPIRIVA capsules should always be stored in the blister and only removed immediately before use. The drug should be used immediately after the packaging over an individual SPIRIVA capsule is opened.

The following packages are available:

- carton containing 5 SPIRIVA capsules (1 unit-dose blister card) and 1 HandiHaler inhalation device (NDC 0597-0075-75)
- carton containing 30 SPIRIVA capsules (3 unit-dose blister cards) and 1 HandiHaler inhalation device (NDC 0597-0075-41)
- carton containing 90 SPIRIVA capsules (9 unit-dose blister cards) and 1 HandiHaler inhalation device (NDC 0597-0075-47)

Storage

Store at 25°C (77°F); excursions permitted to 15°–30°C (59°–86°F) [see USP Controlled Room Temperature].

The SPIRIVA capsules should not be exposed to extreme temperature or moisture. Do not store SPIRIVA capsules in the HandiHaler device.

17 PATIENT COUNSELING INFORMATION

See FDA-approved Patient Labeling

17.1 Instructions for Administering SPIRIVA HandiHaler

It is important for patients to understand how to correctly administer SPIRIVA capsules using the HandiHaler device [see Patient Counseling Information (17)]. Patients should be instructed that SPIRIVA capsules should only be administered via the HandiHaler device and the HandiHaler device should not be used for administering other medications. **The contents of SPIRIVA capsules are for oral inhalation only and must not be swallowed.**

SPIRIVA capsules should always be stored in sealed blisters. Only one SPIRIVA capsule should be removed immediately before use or its effectiveness may be reduced. Additional SPIRIVA capsules that are exposed to air (i.e., not intended for immediate use) should be discarded.

17.2 Paradoxical Bronchospasm

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Patients should be informed that SPIRIVA HandiHaler can produce paradoxical bronchospasm. If paradoxical bronchospasm occurs, patients should discontinue SPIRIVA HandiHaler.

17.3 Urinary Retention

Difficulty passing urine and dysuria may be symptoms of new or worsening prostatic hyperplasia or bladder outlet obstruction. Patients should be instructed to consult a physician immediately should any of these signs or symptoms develop.

17.4 Visual Effects

Eye pain or discomfort, blurred vision, visual halos or colored images in association with red eyes from conjunctival congestion and corneal edema may be signs of acute narrow-angle glaucoma. Patients should be told to consult a physician immediately should any of these signs and symptoms develop. Miotic eye drops alone are not considered to be effective treatment.

Patients should be told that care must be taken not to allow the powder to enter into the eyes as this may cause blurring of vision and pupil dilation.

17.5 Acute Exacerbation

Patients should understand that SPIRIVA HandiHaler is a once-daily maintenance bronchodilator and should not be used for immediate relief of breathing problems (i.e., as a rescue medication).

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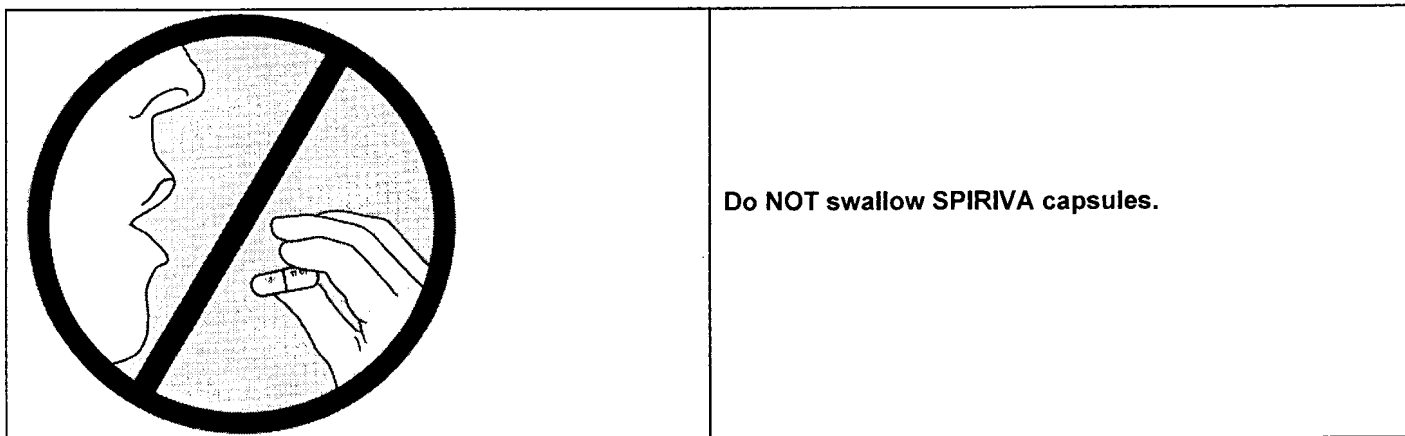
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Patient Information

SPIRIVA® (speh REE vah) HandiHaler®
(tiotropium bromide inhalation powder)



Important Information: Do not swallow SPIRIVA capsules. SPIRIVA capsules should only be used with the HandiHaler device and inhaled through your mouth (oral inhalation).

Read the information that comes with your SPIRIVA HandiHaler before you start using it and each time you refill your prescription. There may be new information. This leaflet does not take the place of talking with your doctor about your medical condition or your treatment.

What is SPIRIVA HandiHaler?

SPIRIVA HandiHaler is a prescription medicine that you use one time every day (a maintenance medicine) to control symptoms of chronic obstructive pulmonary disease (COPD). SPIRIVA HandiHaler helps make your lungs work better for 24 hours. SPIRIVA HandiHaler relaxes your airways and helps keep them open. You may start to feel like it is easier to breathe on the first day, but it may take longer for you to feel the full effects of the medicine. SPIRIVA HandiHaler works best and may help make it easier to breathe when you use it every day.

SPIRIVA HandiHaler also reduces the likelihood of flare-ups and worsening of COPD symptoms (COPD exacerbations). A COPD exacerbation is defined as an increase or new onset of more than one COPD symptom such as cough, mucus, shortness of breath, and wheezing that requires medicine beyond your rescue medicine.

SPIRIVA HandiHaler is **not** a rescue medicine and should not be used for treating sudden breathing problems. Your doctor may give you other medicine to use for sudden breathing problems.

SPIRIVA HandiHaler has not been studied in children.

Who should not take SPIRIVA HandiHaler?

Do not use SPIRIVA HandiHaler if you:

- are allergic to tiotropium. See the end of this leaflet for a complete list of ingredients.
- have had an allergic reaction to ipratropium (Atrovent®).

Allergic reactions may include itching, rash, or swelling of the lips, tongue, or throat (trouble swallowing).

What should I tell my doctor before using SPIRIVA HandiHaler?

Before taking SPIRIVA HandiHaler, tell your doctor about all your medical conditions, including if you:

- have kidney problems.
- have glaucoma. SPIRIVA HandiHaler may make your glaucoma worse.
- have an enlarged prostate, problems passing urine, or a blockage in your bladder. SPIRIVA HandiHaler may make these problems worse.
- are pregnant or plan to become pregnant. It is not known if SPIRIVA HandiHaler could harm your unborn baby.
- are breast-feeding or plan to breast-feed. It is not known if SPIRIVA HandiHaler passes into breast milk. You and your doctor will decide if SPIRIVA HandiHaler is right for you while you breast-feed.

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- have a severe allergy to milk proteins. Ask your doctor if you are not sure.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines and eye drops, vitamins, and herbal supplements. Some of your other medicines or supplements may affect the way SPIRIVA HandiHaler works. SPIRIVA HandiHaler is an anticholinergic medicine. You should not take other anticholinergic medicines while using SPIRIVA HandiHaler, including ipratropium. Ask your doctor or pharmacist if you are not sure if one of your medicines is an anticholinergic.

Know the medicines you take. Keep a list of your medicines with you to show your doctor and pharmacist when you get a new medicine.

How should I take SPIRIVA HandiHaler?

- Use SPIRIVA HandiHaler exactly as prescribed. Use SPIRIVA HandiHaler one time every day.
- Read the "Instructions for Use" at the end of this leaflet before you use SPIRIVA HandiHaler. Talk with your doctor if you do not understand the instructions.
- **Do not swallow SPIRIVA capsules.**
- **Only use SPIRIVA capsules with the HandiHaler device.**
- **Do not use the HandiHaler device to take any other medicine.**
- SPIRIVA HandiHaler comes as a powder in a SPIRIVA capsule that fits the HandiHaler device. Each SPIRIVA capsule, containing only a small amount of SPIRIVA powder, is one full dose of medicine.
- Separate one blister from the blister card. Then take out one of the SPIRIVA capsules from the blister package right before you use it.
- After the capsule is pierced, take a complete dose of SPIRIVA HandiHaler by breathing in the powder by mouth two times, using the HandiHaler device (take 2 inhalations from one SPIRIVA capsule). See the "**Instructions for Use**" at the end of this leaflet.
- Throw away any SPIRIVA capsule that is not used right away after it is taken out of the blister package. Do not leave the SPIRIVA capsules open to air; they may not work as well.
- If you miss a dose, take it as soon as you remember. Do not use SPIRIVA HandiHaler more than one time every 24 hours.
- If you use more than your prescribed dose of SPIRIVA HandiHaler, call your doctor or a poison control center.

What should I avoid while using SPIRIVA HandiHaler?

Do not let the powder from the SPIRIVA capsule get into your eyes. Your vision may get blurry and the pupil in your eye may get larger (dilate). If this happens, call your doctor.

What are the possible side effects of SPIRIVA HandiHaler?

SPIRIVA HandiHaler can cause serious side effects. If you get any of the following side effects, stop taking SPIRIVA HandiHaler and get medical help right away.

- **Allergic reaction.** Symptoms may include: itching, rash, swelling of the lips, tongue, or throat (trouble swallowing).
- **Sudden narrowing and blockage of the airways into the lungs (bronchospasm).** Your breathing suddenly gets worse.
- **New or worsened increased pressure in the eyes (acute narrow-angle glaucoma).** Symptoms of acute narrow-angle glaucoma may include: eye pain, blurred vision, seeing halos (visual halos) or colored images along with red eyes.
- **New or worsened urinary retention.** Symptoms of blockage in your bladder and/or enlarged prostate may include: difficulty passing urine, painful urination.

Other side effects with SPIRIVA HandiHaler include:

- upper respiratory tract infection
- dry mouth
- sinus infection
- sore throat
- non-specific chest pain
- urinary tract infection
- indigestion
- runny nose
- constipation

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- increased heart rate
- blurred vision

These are not all the possible side effects with SPIRIVA HandiHaler. Tell your doctor if you have any side effect that bothers you or that does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How do I store SPIRIVA HandiHaler?

- **Do not store SPIRIVA capsules in the HandiHaler device.**
- Store SPIRIVA capsules in the sealed blister package at room temperature between 68°F–77°F (20°–25°C).
- Keep SPIRIVA capsules away from heat and cold (do not freeze).
- Store SPIRIVA capsules in a dry place. Throw away any unused SPIRIVA capsules that have been open to air.

Ask your doctor or pharmacist if you have any questions about storing your SPIRIVA capsules.

Keep SPIRIVA HandiHaler, SPIRIVA capsules, and all medicines out of the reach of children.

General information about SPIRIVA HandiHaler

Medicines are sometimes prescribed for purposes other than those listed in Patient Information leaflets. Do not use SPIRIVA HandiHaler for a purpose for which it has not been prescribed. Do not give SPIRIVA HandiHaler to other people even if they have the same symptoms that you have. It may harm them.

For more information about SPIRIVA HandiHaler, talk with your doctor. You can ask your doctor or pharmacist for information about SPIRIVA HandiHaler that is written for health professionals.

For more information about SPIRIVA HandiHaler, you may call Boehringer Ingelheim Pharmaceuticals, Inc. at 1-800-542-6257 or (TTY) 1-800-459-9906.

What are the ingredients in SPIRIVA HandiHaler?

Active ingredient: tiotropium

Inactive ingredient: lactose monohydrate

What is COPD (Chronic Obstructive Pulmonary Disease)?

COPD is a serious lung disease that includes chronic bronchitis, emphysema, or both. Most COPD is caused by smoking. When you have COPD, your airways become narrow. So, air moves out of your lungs more slowly. This makes it hard to breathe.

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Instructions for Use

SPIRIVA® (speh REE vah) **HandiHaler®**
(tiotropium bromide inhalation powder)

	Do not swallow SPIRIVA capsules.
--	--

Important Information about using your SPIRIVA HandiHaler

- **Do not swallow SPIRIVA capsules.**
- **SPIRIVA capsules should only be used with the HandiHaler device and inhaled through your mouth (oral inhalation).**
- **Do not use your HandiHaler device to take any other medicine.**

First read the Patient Information, then read these Instructions for Use before you start to use SPIRIVA HandiHaler and each time you refill your prescription. There may be new information.

Becoming familiar with your HandiHaler device and SPIRIVA capsules:

Your SPIRIVA HandiHaler comes with SPIRIVA capsules in blister packaging and a HandiHaler device. Use the new HandiHaler device provided with your medicine.

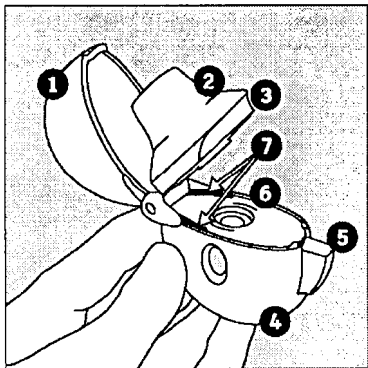


Figure A

The parts of your HandiHaler device include:
(See Figure A)

1. dust cap (lid)
2. mouthpiece
3. mouthpiece ridge
4. base
5. green piercing button
6. center chamber
7. air intake vents

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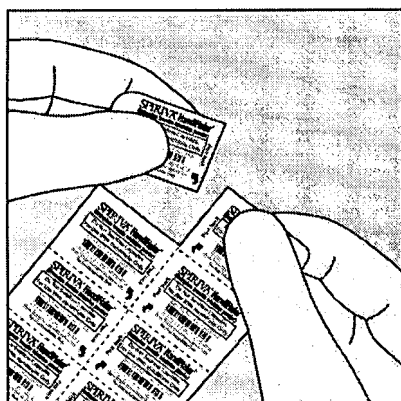


Figure B

Each SPIRIVA capsule is packaged in a blister. (See Figure B)

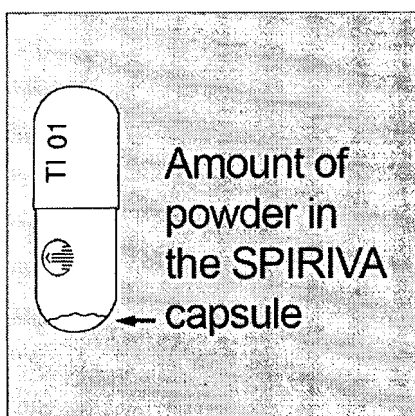


Figure C

- Each SPIRIVA capsule contains only a small amount of powder. (See Figure C) This is 1 full dose.
- **Do not open the SPIRIVA capsule** or it may not work.

Taking your full daily dose of medicine requires 4 main steps.

Step 1. Opening your HandiHaler device:

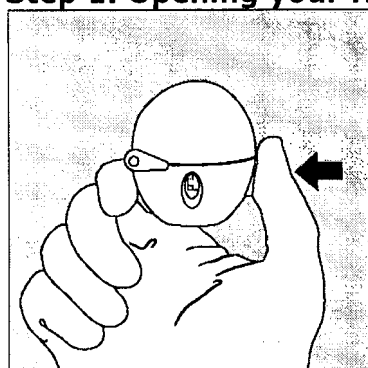


Figure D

After removing your HandiHaler device from the pouch:

- Open the dust cap (lid) by pressing the green piercing button. (See Figure D)

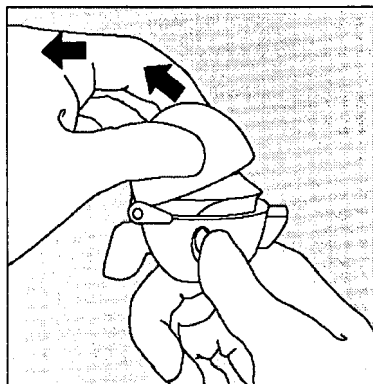


Figure E

- Pull the dust cap (lid) upwards away from the base to expose the mouthpiece. (See Figure E)

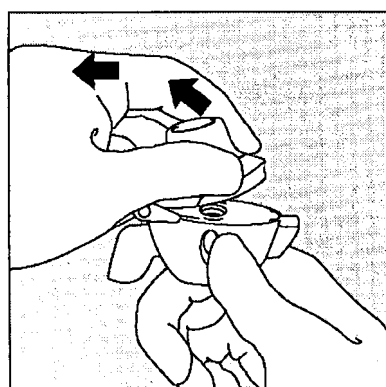


Figure F

- Open the mouthpiece by pulling the mouthpiece ridge up and away from the base so the center chamber is showing. (See Figure F)

Step 2. Inserting the SPIRIVA capsule into your HandiHaler device:

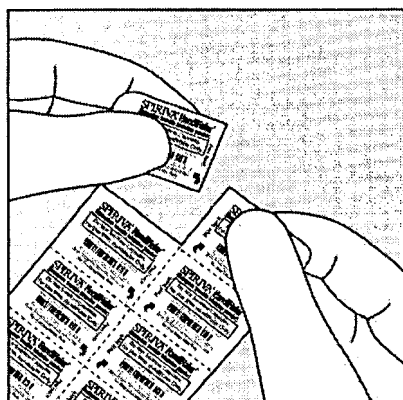


Figure G

Each day, separate only 1 of the blisters from the blister card by tearing along the perforated line. (See Figure G)

Remove the SPIRIVA capsule from the blister:

- **Do not** cut the foil or use sharp instruments to take out the SPIRIVA capsule from the blister.

Step 3. Piercing the SPIRIVA capsule:

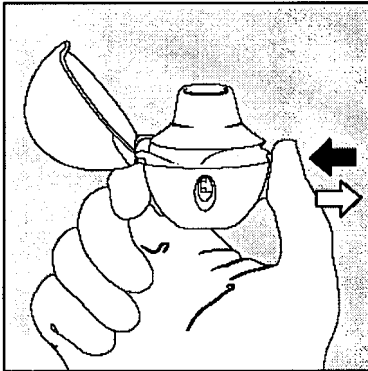


Figure K

- Hold your HandiHaler device with the mouthpiece pointed up. (See Figure K)
- Press the green piercing button once until it is flat (flush) against the base, then release. This is how you make holes in the SPIRIVA capsule so that you get your medicine when you breathe in.
- **Do not** press the green button more than one time.
- **Do not** shake your HandiHaler device.
- The piercing of the SPIRIVA capsule may produce small gelatin pieces. Some of these small pieces may pass through the screen of your HandiHaler device into your mouth or throat when you breathe in your medicine. This is normal. The small pieces of gelatin should not harm you.

Step 4. Taking your full daily dose (2 inhalations from the same SPIRIVA capsule):

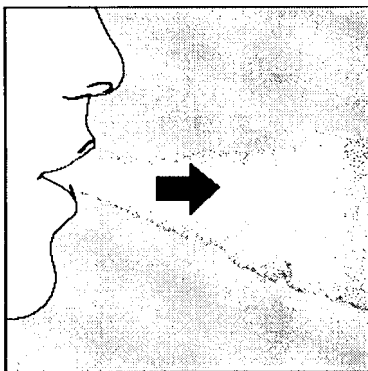


Figure L

Breathe out completely in 1 breath, emptying your lungs of any air. (See Figure L)

Important: Do not breathe into your HandiHaler device.

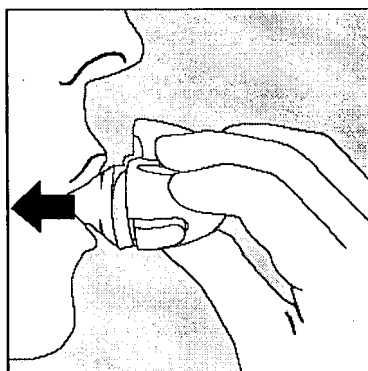


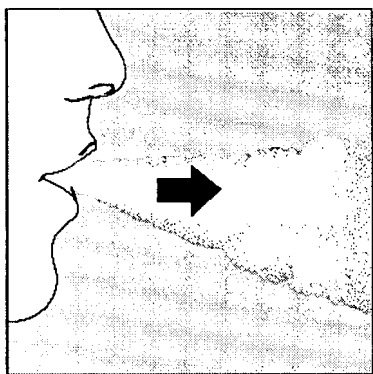
Figure M

With your next breath, take your medicine:

- **Hold your head in an upright position while you are looking straight ahead.** (See Figure M)
- Raise your HandiHaler device to your mouth in a horizontal position. **Do not** block the air intake vents.
- Close your lips tightly around the mouthpiece.
- **Breathe in deeply** until your lungs are full. You should **hear or feel the SPIRIVA capsule vibrate (rattle)**. (See Figure M)
- Hold your breath for a few seconds and, at the same time, take your HandiHaler device out of your mouth.
- Breathe normally again.

The rattle tells you that you breathed in correctly. If you do not hear or feel a rattle, see the section, "If you do not hear

or feel the SPIRIVA capsule rattle as you breathe in your medicine.”



Figure

N

To get your full daily dose, you must again, breathe out completely (See Figure N) and for a second time, breathe in (See Figure O) from the same SPIRIVA capsule.

Important: Do not press the green piercing button again.

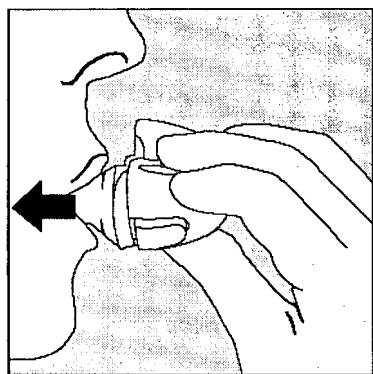


Figure O

Remember: To get your full medicine dose each day, you must breathe in 2 times from the same SPIRIVA capsule. Make sure you breathe out completely each time before you breathe in from your HandiHaler device.

Caring for and storing your SPIRIVA HandiHaler:

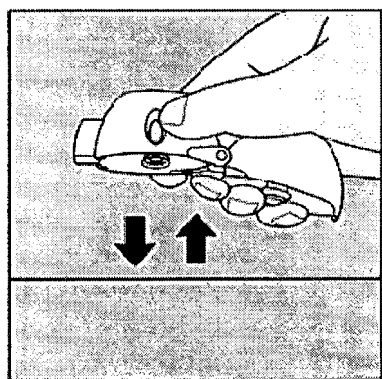


Figure P

- After taking your daily dose, open the mouthpiece and tip out the used SPIRIVA capsule into your trash can, without touching it.
- Remove any SPIRIVA capsule pieces or SPIRIVA powder buildup by turning your HandiHaler device upside down and gently, but firmly, tapping it. (See Figure P) Then, close the mouthpiece and dustcap for storage.
- **Do not** store your HandiHaler device and SPIRIVA capsules (blisters) in a damp moist place. Always store SPIRIVA capsules in the sealed blisters.

If you do not hear or feel the SPIRIVA capsule rattle as you breathe in your medicine:

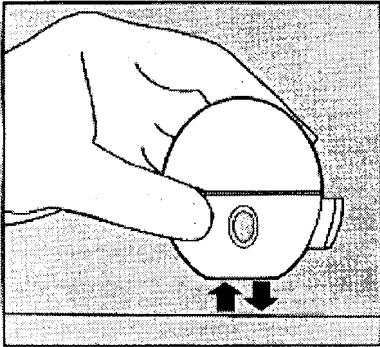


Figure Q

Do not press the green piercing button again.

Hold your HandiHaler device with the mouthpiece pointed up and tap your HandiHaler device gently on a table. (See Figure Q)

Check to see that the mouthpiece is completely closed. Breathe out completely before deeply breathing in again with the mouthpiece in your mouth. (See Figure O)

If you still do not hear or feel the SPIRIVA capsule rattle after repeating the above steps:

- Throw away the SPIRIVA capsule.
- Open the base by lifting the green piercing button and check the center chamber for pieces of the SPIRIVA capsule. SPIRIVA capsule pieces in the center chamber can cause a SPIRIVA capsule not to rattle.
- Turn your HandiHaler device upside down and gently, but firmly, tap to remove the SPIRIVA capsule pieces. Call your doctor for instructions.

Cleaning your HandiHaler device:

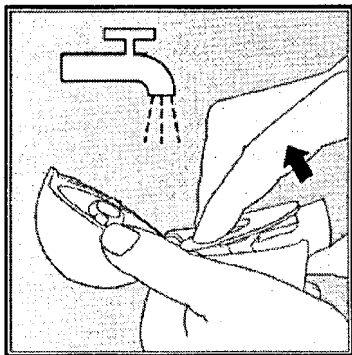


Figure R

Clean your HandiHaler device as needed. (See Figure R)

- **It takes 24 hours to air dry your HandiHaler device** after you clean it.
- **Do not** use cleaning agents or detergents.
- **Do not** place your HandiHaler device in the dishwasher for cleaning.

Cleaning Steps:

- Open the dust cap and mouthpiece
- Open the base by lifting the green piercing button.
- Look in the center chamber for SPIRIVA capsule pieces or powder buildup. If seen, tap out.
- Rinse your HandiHaler device with warm water, pressing the green piercing button a few times so that the center chamber and the piercing needle is under the running water. Check that any powder buildup or SPIRIVA capsule pieces are removed.
- Dry your HandiHaler device well by tipping the excess water out on a paper towel. Air-dry afterwards, leaving the dust cap, mouthpiece, and base open by fully spreading it out so that it dries completely.
- **Do not** use a hair dryer to dry your HandiHaler device.
- **Do not** use your HandiHaler device when it is wet. If needed, you may clean the outside of the

mouthpiece with a clean damp cloth.

Helpful Hints to help ensure that you are properly taking your full daily dose of SPIRIVA HandiHaler:

- **Press** the green piercing button **1 time**; **Breathe in 2 times**; **Breathe out completely** before each of the 2 inhalations.
- Always use the new HandiHaler device provided with your medicine.
- Keep your HandiHaler device with the mouthpiece pointed up when pressing the green piercing button.
- **Press the green piercing button 1 time** to pierce the SPIRIVA capsule.
- Do not breathe out into your HandiHaler device.
- Keep your HandiHaler device in a horizontal position and keep your head upright, looking straight ahead, when breathing in.
- Check the center chamber of your HandiHaler device for SPIRIVA capsule pieces or powder build-up. If pieces or powder are seen, tap out before use.
- Clean your HandiHaler as needed and dry thoroughly.

For more information, ask your doctor or pharmacist, or go to www.spiriva.com or call 1-800-XXX-XXX.

This Instructions for Use has been approved by the U.S. Food and Drug Administration.

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Ridgefield, CT 06877 USA

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DIRECCIÓN DE NUEVAS CREACIONES
SOLICITUD FASE NACIONAL - PCT

1	TIPO SE SOLICITUD	☒ Patente de invención ☒ Capítulo I	☐ Patente de Modelo de Utilidad ☐ Capítulo II
2	DATOS SOLICITUD INTERNACIONAL PCT (86)		
Solicitud Internacional No.		PCT/	Fecha
Publicación Internacional No.		WO	Fecha
3	TÍTULO DE LA INVENCIÓN (200 caracteres o espacios máximos)		
PARTICULAS INHALABLES QUE COMPRENDEN UNA FORMA ANHIDRA AMORFA DE TIOTROPIO ESTABILIZADA CON UN AGENTE ESTABILIZANTE QUE ES UN DERIVADO DE AZUCAR, COMPOSICIONES FARMACEUTICAS QUE LAS CONTIENEN Y PROCEDIMIENTO PARA SU PREPARACION			
4	CLASIFICACIÓN INTERNACIONAL (CIP)		
A61K 9/00			
5	SOLICITANTE (S) ☐ Esta persona también es inventor. Para datos adicionales utilizar hoja de información complementaria		
APELLIDOS O RAZÓN SOCIAL		NOMBRE	IDENTIFICACIÓN
LABORATORIOS LICONSA, S.A.			
6	DATOS DEL SOLICITANTE		
DIRECCIÓN		No. TELÉFONO	
Gran Vía Carles III, 98 Ed. Trade			
CIUDAD		CORREO ELECTRÓNICO	
Barcelona,			
DEPARTAMENTO/ESTADO		NACIONALIDAD O	
		LUGAR DE	
PAÍS DE RESIDENCIA/		CONSTITUCIÓN	
España		España	
7	INVENTOR (ES) Para datos adicionales utilizar hoja de información complementaria		
APELLIDOS		NOMBRES	NACIONALIDAD
1	AMIGHI	Karim	Bélgica
2	SERENO GUERRA	Antonio	Bélgica
3			
4			
DIRECCIÓN DE CORREO ELECTRÓNICO:			
8	DATOS INVENTOR (ES)		
PAÍS RESIDENCIA		DEPARTAMENTO/ESTADO	CIUDAD
1	Bélgica		Bruselas
2	Bélgica		Melsbroeck
3			
4			
DIRECCIÓN			
Clos Alberto Santos Dumont, 8			
C. Pasiewijk, 21			
OTRO(S) SOLICITANTE(S) Y/O (OTRO(S)) INVENTOR(ES)			
☐ Los demás solicitantes y/o (demás) inventores se indican en una hoja a continuación			
9	☐ REPRESENTANTE LEGAL ☒ APODERADO		
APELLIDOS		NOMBRES	IDENTIFICACION
CASTILLO GIBSONE		LUIS FELIPE	C.C. 79.397.879 de T.P. 68.995
			Bogotá del C.S.J.
DIRECCIÓN		No. TELÉFONO	
Carrera 13 No. 37 - 43 Piso 12			
CIUDAD		CORREO ELECTRÓNICO	
Bogotá D.C.		info@castillogra	
		u.com	
PAÍS		No. RADICACIÓN O PORTOCOLO DE PODER GENERAL	
Colombia			

40

10

DECLARACIONES DE PRIORIDAD

SI

NO

(33)PAIS DE ORIGEN

1EP

2E.U.A.

3

CÓDIGO PAÍS

(31) NÚMERO

08382040.7

61/104,113

(32) FECHA (AAAA/MM/DD)

02.10.2008

09.10.2008

11

DECLARACIÓN SOBRE USO DE RECURSOS GENÉTICOS O BIOLÓGICOS

Declaro que el objeto de la presente solicitud de patente fue obtenido a partir de recursos genéticos o biológicos de los que cualquiera de los países miembros de la Comunidad Andina es país de origen,

SI

X

NO

Nota: En caso afirmativo deberá anexar copia del contrato de acceso de recursos genéticos o productos derivados, o certificado o número de registro, expedido por la Autoridad competente,

12

DECLARACION SOBRE USO DE CONOCIMIENTOS TRADICIONALES

Declaro que el objeto de la presente solicitud de patente fue obtenido a partir de conocimientos tradicional de comunidades indígenas, afroamericanas o locales de países miembros de la Comunidad Andina.

SI

X

NO

Nota: En caso afirmativo deberá anexar la licencia o autorización de uso de conocimiento tradicional, o certificado o número de registro expedido por la Autoridad competente.

13

REDUCCIÓN DE TASAS

Declaro que carezco de medios económicos para presentar la solicitud de la patente.

SI

X

NO

Nota: En caso de ser persona natural y carecer de medios económicos, y por lo tanto, aplique la reducción de tasas a que se refiere la resolución vigente en tarifas, debe firmar la presente solicitud bajo la gravedad de juramento.

Micro, pequeñas y medianas empresas

Universidades públicas o privadas

Entidades sin ánimo de lucro

Debe aportar los documentos que se indican en el numeral 17 de anexos

14

AUTORIZACION DE NOTIFICACIÓN EN LÍNEA

SI

X

NO

Manifiesto que he leído y entendido perfectamente los términos y condiciones de uso de medios electrónicos para las notificaciones en línea a través de internet de los actos administrativos proferidos por la Superintendencia de Industria y Comercio que deben ser notificados personalmente y, en consecuencia, autorizo el servicio de notificación a través de internet.

15

COMPROBANTE DE PAGO O PAGO ELECTRÓNICO

No.

Fecha

16

FIRMA DEL SOLICITANTE, DEL APODERADO O DEL REPRESENTANTE LEGAL

Junto a cada firma, indicar el nombre del firmante y su calidad (si tal calidad no es obvia al leer el petitorio)

LUIS FELIPE CASTILLO GIBSONE

17

ANEXOS

Documentación Técnica

Solicitud Internacional en Castellano

1

X

Descripción

No. De folios:

2

X

Reivindicaciones

No. Reivindicaciones:

3

X

Dibujos y/o figuras

No. Folios:

4

Resumen

5

Certificado de depósito de material biológico si fuera el caso

6

Listado de secuencias de nucleótidos y/o aminoácidos en forma digital si fuera el caso

7

Arte final 12 x 12

8

Anexo formato digital

Documentación Jurídica

9

X

Poderes, si fuera el caso.

10

Documento que legalmente pruebe la cesión del inventor al solicitante o a su causante

11

Copia del contrato de acceso de recursos genéticos o productos derivados, o certificado número de registro, si fuera al caso

12

Copia de la licencia o autorización de conocimientos Tradicionales, o certificado o número de registro, si fuera el caso

13

Reducción de tasas

Micro, pequeñas o medianas empresas

Copia simple de la declaración de renta del año inmediatamente anterior, o en su defecto prueba documental idónea

Documento de constancia de cumplimiento con lo establecido en la ley 905 de 2004

Universidades públicas o privadas

Copia acto de reconocimiento institucional emitido por el Ministerio de Educación

Entidades sin animo de lucro

Copia de regido vigente en Cámara de comercio

Hoja de información complementaria

16

X

Comprobante de pago de la tasa de presentación de la solicitud

17

Comprobante de pago por reivindicación de prioridad

18

Comprobante de pago de la tasa de concepto de excedente de palabras en la publicación

19

Comprobante de pago por reivindicación adicional a 10

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
NIT : 800.176.089-2
- / -

41

 Industria y Comercio SUPERINTENDENCIA	RECIBO DE CAJA	No. 13 - 0020690
		Bogotá D.C., Febrero 28 de 2013 - 15:51:20

RECIBIDO DE : CASTILLO GRAU & ASOCIADOS LTDA. NI 800.098.704

*** Soporte del Pago ***					
TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	VR. PAGO
CONSIGNACION	BANCO DE BOGOTA	062754387	556974375	28/02/2013	886.000.00

*** Conceptos Pagados ***			
CANT.	RENTISTICO	CONCEPTO	Vr.UNDITARIO Vr.CONCEPTO
5	50005-01-01 SOLICITUDES	1607 REIVINDICACION PATENTE UNITARIA ADICIONAL A LAS 10 INIC	30.000.00 150.000.00
			\$150.000.00
			=====

SON: **CIENTO CINCUENTA MIL PESOS MONEDA CORRIENTE**

Responsable: 

Recibo de Caja Aplicado al Expediente No. _____

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 11-052660- -00008-0000

Fecha: 2013-02-28 16:57:32 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 523 RESPUESTA Folios: 41



Industria y Comercio
SUPERINTENDENCIA

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

SOLICITUD
PATENTE DE INVENCION

21. **EXPEDIENTE No.** _____

54. **TÍTULO** PARTICULAS INHALABLES QUE COMPRENDEN UNA FORMA ANHIDRA AMORFA DE
TIOTROPIO ESTABILIZADA CON UN AGENTE ESTABILIZANTE QUE ES UN DERIVADO DE AZUCAR
COMPOSICIONES FARMACEUTICAS QUE LAS CONTIENEN Y PROCEDIMIENTO PARA SU PREPARACION

51. **CLASIFICACIÓN INTERNACIONAL** A61K 9/00

71. **SOLICITANTE** LABORATORIOS LICONSA, S.A.

DOMICILIO BARCELONA, ESPAÑA

74. **APODERADO** LUIS FELIPE CASTILLO

22. **BOGOTÁ, D.C.,** _____