



No. 07-136831-00004-0000

Fecha: 2009-07-01 16:37:15 Dep. 2020 NUECREACIONE  
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI  
Act. 400 OPOSIOBSERVTER Folios: 64

FORMULARIO ÚNICO DE OPOSICIÓN

62  
64

①

OPOSICION A:

- |                                                                        |                                                  |
|------------------------------------------------------------------------|--------------------------------------------------|
| <input checked="" type="checkbox"/> Patente de Invencion.              | <input type="checkbox"/> Marca Colectiva.        |
| <input type="checkbox"/> Patente de Modelo de Utilidad.                | <input type="checkbox"/> Marca de Certificación. |
| <input type="checkbox"/> Diseño Industrial.                            | <input type="checkbox"/> Lema Comercial.         |
| <input type="checkbox"/> Esquema de Trazado para Circuitos Integrados. |                                                  |
| <input type="checkbox"/> Marcas de Productos o Servicios.              |                                                  |

②

Número del expediente: 07 136.831

Solicitante: SANOFI AVENTIS

SOLICITUD  
PUBLICADA

Apoderado: EMILIO FERRERO

Título de la nueva creación o denominación del signo: FORMULACION DE  
LIBERACION PROLONGADA DE PRINCIPIOS ACTIVOS QUE PRESENTAN UNA SOLUBILIDAD  
DEPENDIENTE DEL PH.

Gaceta: 602

③ OPOSICIÓN PRESENTADA POR:

|                              |                                               |                                          |                                         |
|------------------------------|-----------------------------------------------|------------------------------------------|-----------------------------------------|
| SOLICITANTE                  | Nombre: GYNOPHARM S.A. ✓                      | IDENTIFICACIÓN                           |                                         |
|                              | Dirección: Carrera 14 N° 94-44 Piso 7 Torre b | C.C. <input type="checkbox"/>            | NIT <input checked="" type="checkbox"/> |
|                              | Nacionalidad o Domicilio: COLOMBIA            | C.E. <input type="checkbox"/>            | Otro <input type="checkbox"/>           |
|                              | Lugar de Constitución: BARRANQUILLA           | Cual _____                               |                                         |
|                              | Telefono: 2 36 84 95 Fax: _____               | Numero 802,006,279-4                     |                                         |
|                              | E-mail: _____                                 |                                          |                                         |
| REPRESENTANTE<br>O APODERADO | Nombre: ELIANA ISAURA MORENO<br>BOHORQUEZ     | IDENTIFICACIÓN                           |                                         |
|                              | Dirección: CARRERA 13 No. 119-95              | C.C. <input checked="" type="checkbox"/> | NIT <input type="checkbox"/>            |
|                              | Telefono: (571)213 12 13 Fax: (571)612 19 79  | C.E. <input type="checkbox"/>            | Otro <input type="checkbox"/>           |
|                              | E-mail: negocios@optimum-co.com               | Cual _____                               |                                         |
|                              |                                               | Numero 51.975.664 TP 83823               |                                         |

④ FUNDAMENTOS DE LA OPOSICIÓN:

Art.14, 16, 18, 20 y 30 de la Decisión 486 de la CAN

Causal: No cumple con los requisitos de patentabilidad.

Signo opositor: \_\_\_\_\_

Justificación: \_\_\_\_\_

La presente solicitud no cumple con los requisitos de patentabilidad dado que lo  
revelado, ya se encontraba en el estado de la técnica o es posible derivarlo de la  
misma tal y como se demostrará en el capítulo "Fundamento de Hechos".

⑤ Comprobante de pago No. \_\_\_\_\_

Fecha \_\_\_\_\_

⑥ ANEXOS

- ☒ Comprobante de pago de la tasa.
- ☒ Poderes, si fuere el caso.
- ☒ Pruebas de los fundamentos de la oposición.
- ☐ Documentos que acrediten el legítimo interés, si fuere el caso.
- ☒ Documento que acredita la existencia y representación legal de las partes, cuando sean personas jurídicas.

67

⑦

NOMBRE: ELIANA ISAURA MORENO BOHORQUEZ ✓

FIRMA: *Eliana* ✓

C.C. 51.975.664

TP. 83823

(54) 60 ✓

PH", cuyo titular es SANOFI AVENTIS, y pido a Usted declarar fundada esta oposición y en consecuencia negar el registro de la patente solicitada.

### 1. INTERÉS PARA ACTUAR ✓

Conforme a lo dispuesto en el artículo 42 de la Decisión 486 de 2000 de la CAN, estando dentro del término estipulado por la ley, manifiesto el legítimo interés de nuestra representada para oponerse al registro de la patente de la referencia, atendiendo a que la solicitud pretendida no cumple con los requisitos dispuestos en la ley como se analizará más adelante y de ser concedida afectaría directamente la comercialización de algunos productos de mi representada, que contienen, en particular zolpidem. Por lo tanto, solicito respetuosamente a ese Despacho se sirva tener en cuenta la presente oposición dentro del trámite administrativo que se surte en esta Superintendencia.

### 2. FUNDAMENTOS DE HECHOS

2.1. La solicitud objeto de la presente fue presentada el 11 de enero de 2008 reivindicando prioridad bajo la solicitud FR20050006539 del 2005-06-28; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 602 del 31 de Marzo de 2009, cuya publicación internacional corresponde a la WO2007003746 del 2007-01-11.

2.2. La solicitud colombiana 07 136831 objeto de la presente oposición, se refiere a una formulación nueva para una liberación prolongada de un principio activo que presenta una solubilidad dependiente del pH. La formulación de la invención

Señora Jefe,

DIVISIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Referencia : Expediente N° 07 136831

Asunto : Oposición a la solicitud de patente de Invención titulada  
"FORMULACIÓN DE LIBERACIÓN PROLONGADA  
DE PRINCIPIOS ACTIVOS QUE PRESENTAN UNA  
SOLUBILIDAD DEPENDIENTE DEL PH"

Solicitante : SANOFI AVENTIS

Opositora : GYNOPHARM S.A.

Publicada en la Gaceta de la Propiedad Industrial

N° 602 del 31 de Marzo de 2009

Yo, **ELIANA ISAURO MORENO BOHORQUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del Consejo Superior de la Judicatura, en mi condición de apoderada de la sociedad **GYNOPHARM S.A.** conformada bajo las leyes de la República de Colombia y domiciliada en la ciudad de Barranquilla, Colombia, atentamente manifiesto que estando dentro del término de ley y por orden expresa de mi representada, presento oposición a la concesión del registro de la Patente de Invención titulada "FORMULACION DE LIBERACION PROLONGADA DE PRINCIPIOS ACTIVOS QUE PRESENTAN UNA SOLUBILIDAD DEPENDIENTE DEL

comprende un excipiente matricial a base de polímero hidrófilo que contiene una dosis determinada del principio activo, y también comprende uno o varios agentes acidificantes en forma de una sal ácida de un ácido orgánico.

2.3. Ahora bien, con base en el artículo 14 de la Decisión 486 de la CAN consagra lo siguiente: *"Los países miembros otorgarán patentes para las invenciones, sean de producto o procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"*. Así las cosas, las invenciones objeto de patente deben ser nuevas y tener nivel inventivo. Bien, pues antes de la fecha de prioridad de esta solicitud se encuentran los siguientes documentos que afecta la patentabilidad de la presente solicitud:

- D1: WO0033835 publicada el 15 de junio de 2000.

2.4. Ahora bien, el documento D1, particularmente en la descripción se relaciona con formas de dosificación de liberación controlada de zolpidem o sus sales para liberar zolpidem sobre un periodo de tiempo predeterminado, según un perfil bifásico de disolución, donde la primera fase es una fase de liberación inmediata y la segunda fase es una fase de liberación prolongada. Particularmente, en la descripción se definen comprimidos de liberación controlada que comprenden zolpidem, un derivado de celulósico y un ácido orgánico seleccionado de ácido tartárico, ácido málico, ácido fumárico, ácido láctico, ácido cítrico, ácido adípico y ácido succínico, así como sus sales. Esto se define claramente en dicha anterioridad D1 en la página 8, a partir de la línea 4 donde se define su disolución independiente del pH y donde los ácidos orgánicos aceptables de la misma se ejemplifican a partir de la línea 11 a la línea 17 de dicha página 8. Así las cosas, como lo evidencia dicho documento D1, la presente solicitud no es novedosa pues lo revelado ya se encontraba en el estado de la técnica.

169  
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2.5. Por lo tanto, este documento objeto de oposición a la luz del documento D1 carece evidentemente de NOVEDAD.

2.6. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 07 136831 no puede pretender un monopolio por patente toda vez que lo que pretende no cumple con uno de los tres requisitos necesarios para su protección.

2.7. Que por consiguiente, respecto a la solicitud pretendida se tiene que:

2.7.1. CARECE DE NOVEDAD: Según la decisión 486 de la Comunidad Andina de Naciones, Artículo 16.- *"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica. El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida."* A la fecha de prioridad, 28 de junio de 2005 ya era conocido, pues como se demostró, era parte del arte anterior con base en el documento D1, la dosis de liberación controlada de un activo que comprende además un excipiente matricial a base de polímero hidrófilo que comprende uno o varios agentes acidificantes en forma de una sal ácida de un ácido orgánico, sobre el cual busca protección en el capítulo reivindicatorio.

2.8. Dado lo anterior, es posible deducir que la solicitud y lo reivindicado no es objeto de patentabilidad pues es contrario a lo que dicta la Decisión 486 de la Comunidad Andina de Naciones, Artículo 14.- *"Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación"*

industrial.” La solicitud pretendida no cumple con uno de los tres requisitos de patentabilidad.

- 2.9. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y negar el registro Patente de invención denominada **FORMULACIONES DE LIBERACION PROLONGADA DE PRINCIPIOS ACTIVOS QUE PRESENTAN UNA SOLUBILIDAD DEPENDIENTE DEL PH**”, cuyo titular es SANOFI AVENTIS, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 602 del 31 de Marzo de 2009.

### 3. PRUEBAS

De conformidad con lo dispuesto por las normas vigentes, solicito a usted tener como prueba en este asunto los siguientes:

- DI: W00033835 publicada el 15 de junio de 2000.

### 4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

- 4.1. Numeral 1 del artículo 586 del Código de Comercio.

6. NOTIFICACIONES

Para efectos de notificaciones que por disposición del artículo 50 del Decreto 01 de 1984 debe hacer su Despacho, informo que mi representada y la suscrita recibiremos notificaciones en la Secretaría de su Despacho o en mis oficinas situadas en la Carrera 13 N° 119-95, Of. 104 de esta ciudad de Bogotá.

Señor Superintendente,



ELIANA ISAURO MORENO BOHORQUEZ

C.C. 51'975.664 de Bogotá

T.P.A. 83823 del C.S. de la J.

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**PODER ESPECIAL**

Yo, **LUIS PALACIOS ARAGÓN**, mayor de edad y vecino de la ciudad de Barranquilla (Colombia), identificado como aparece al pie de mi firma, quien en el presente documento actúa en calidad de Representante Legal de la sociedad **GYNOPHARM S.A.** sociedad legalmente constituida y domiciliada en la ciudad de Barranquilla (Colombia), por el presente documento otorgo a la doctora **ELIANA ISAURA MORENO BOHÓRQUEZ**, abogada en ejercicio, identificada como aparece al pie de su firma, con tarjeta profesional No. 83823 del C.S. de la J., poder especial, amplio y suficiente, para formular oposiciones u observaciones a la solicitud de patente No. 08 136831, titulada **"FORMULACIONES DE LIBERACION PROLONGADA DE PRINCIPIOS ACTIVOS QUE PRESENTAN UNA SOLUBILIDAD DEPENDIENTE DEL PH"**, cuyo titular es **SANOFI AVENTIS**, publicada en la gaceta No. 602 del 31 de marzo de 2009.

Nuestro apoderado queda facultado, de manera expresa, para realizar todo tipo de actos necesarios para llevar a cabo el trámite de la oposición, incluyendo, sin limitación, preparar y presentar solicitudes, hacer declaraciones, pagar tasas, contribuciones e impuestos, recabar los títulos o certificados. Asimismo quedan autorizados para impugnar administrativa y judicialmente todo lo que fuere resuelto en el expediente a que se hace expresa referencia en el presente poder, con todas las facultades generales y específicas que fuera requerido para ella.

De la misma manera, además de las facultades que le confiere la naturaleza del presente mandato, se encuentran facultados para recibir, desistir, transigir, sustituir, y reasumir el presente poder, incoar acciones, interponer recursos y demás facultades conferidas por la ley.

Dado y Firmado en Barranquilla (Colombia) a los \_\_\_\_ días del mes de \_\_\_\_ de 2009.

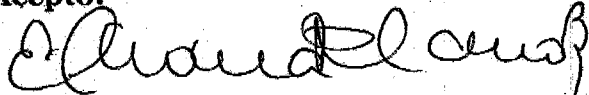
**GYNOPHARM S.A.**

Cédula de Extranjería: No. 319788.

NIT: 802.006479-4

Representante Legal

Acepto:



**ELIANA ISAURA MORENO BOHÓRQUEZ**

C.C. 51'975.664 de Bogotá

T.P.A. 83823 del C.S. de la J.

**RECONOCIMIENTO DE DOCUMENTO PRIVADO**

Ante mí. LILIANA CONSTANZA BARBOSA PLATA,  
 Notaria Veinticinco del Circuito de Bogotá (E),  
 comparece Guillermo Alberto Palacios  
Aragon  
 identificado con cédula de ciudadanía  
CE 39788  
 y declara que la firma puesta en el presente  
 instrumento privado es suya y que el contenido  
 del mismo es verdadero.  
 Bogotá D.C. **16 JUN. 2009**  
 FIRMA [Firma]  
LILIANA CONSTANZA BARBOSA PLATA  
 NOTARIA VEINTICINCO DEL CIRCUITO DE BOGOTÁ

**NOTARIA PRIMERA DE CHIA  
 PRESENTACION PERSONAL**

Este memorial dirigido a Superintendencia de Industria y Comercio

fué presentado personalmente ante el suscrito notario por Eliona Isaura

Moledo Bohorquez.

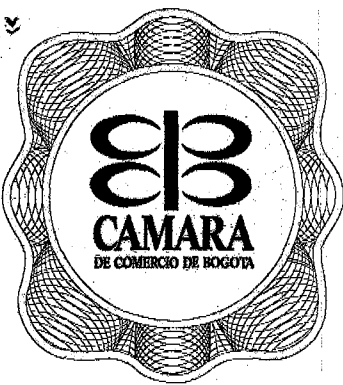
Identificado C.C. 519.25669 Bogotá

T.P. de Abogado No. 83823

Chía 01 JUL. 2009

[Firma]





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CERTIFICADO NACIONAL  
CAMARA DE COMERCIO DE BARRANQUILLA  
FECHA: 2009/06/19 HORA: 13:11:00  
OPERACION: 10ERP0619107 PAGINA: 1

**CERTIFICADO DE EXISTENCIA Y REPRESENTACION LEGAL O DE INSCRIPCION DE DOCUMENTOS.**

EL SUSCRITO SECRETARIO DE LA CAMARA DE COMERCIO DE BARRANQUILLA, CON FUNDAMENTO EN LAS INSCRIPCIONES DEL REGISTRO MERCANTIL:

**C E R T I F I C A**

Que por Escritura Pública No. 3,551 del 17 de Dic/bre de 1997 otorgada en la Notaria 3a. de Barranquilla, inscrito(as) en esta Cámara de Comercio, el 18 de Dic/bre de 1997 bajo el No. 72,965 del libro respectivo, fue constituida la sociedad-----  
anonima denominada GYNOPHARM S.A.-----

**C E R T I F I C A**

Que dicha sociedad ha sido reformada por las siguientes escrituras y/o documentos privados:

Numero aaaa/mm/dd Notaria No. Insc o Reg aaaa/mm/dd  
532 1999/03/25 Notaria 3a. de Barranquilla 80,373 1999/04/13

**C E R T I F I C A**

Que de acuerdo con la(s) escritura(s) arriba citada(s), la sociedad se rige por las siguientes disposiciones:

DENOMINACION O RAZON SOCIAL:

GYNOPHARM S.A.-----

DOMICILIO PRINCIPAL: Barranquilla.

NIT No: 802.006.279-4.

MATRICULA MERCANTIL: 245,470.

**C E R T I F I C A**

Dirección para notificaciones judiciales:

CR 49 C No 80 - 125 OF 512.

De la ciudad de Barranquilla.

**C E R T I F I C A**

DURACION: El término de duración de la sociedad se fijó hasta el 16 de Dic/bre de 2047.

**C E R T I F I C A**

OBJETO SOCIAL: a) La fabricacion de capsulas y otro productos similares a partir de materiales tales como gelatinas u otros de distinta naturaleza, que puedan ser utilizados como envases o recipientes de productos y sustancias quimicas, farmaceuticas y cosmeticas, para

\*\*\* CONTINUA \*\*\*

PREMIO  
COLOMBIANO  
A LA CALIDAD  
DE LA GESTION

IMPRESO POR BARRANQUILLA S.A. NIT 802.006.279-4

# CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2009/06/19

HORA: 13:11:00

OPERACION: 10ERP0619107

PAGINA: 2

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 uso y consumo humano y veterinario. b) La investigacion, desarrollo y fabricacion de toda clase de productos y sustancias quimicas, farmaceuticas y cosmeticas para uso y consumo humano, animal y vegetal. c) La compra y venta de materias primas, insumos y productos intermedios necesarios para los procesos de fabricacion de sustancias quimicas, farmaceuticas y cosmeticas, asi como la comercializacion interna y externa de los productos terminados. d) La compra, venta, importacion, exportacion y distribucion de toda clase de elementos instrumentales y equipos, medicos, quirurgicos, odontologicos y hospitalarios para la salud humana y animal. e) Actuar como representante o agente de personas naturales y juridicas nacionales y extranjeras en la realizacion de operaciones o transacciones relacionadas con la industria farmaceutica y en especial con cualesquiera de las actividades descritas en los literales a), b), c) y d) antes transcritos. f) Prestar los servicios de asesoria y consultoria en las areas administrativa, de mercadeo, analisis clinico, asistencia tecnica, investigacion, costos y produccion exportaciones, importaciones, ventas, relacionadas con iguales o similares actividades a las que constituyen el objeto de GYNOPHARM S.A., asi como los de publicidad y promocion de productos quimicos, cosmeticos y farmaceuticos para uso humano, animal o industrial. g) Adquirir, operar, administrar y explotar, a cualquier titulo, empresas o establecimientos dedicados a la investigacion, desarrollo, fabricacion o comercializacion de productos quimicos, farmaceuticos, hospitalarios o cosmeticos. En desarrollo de su objeto principal, la sociedad podra tomar interes social como accionista, socio o fundador de empresas que tengan igual o similar objeto; comprar, vender, importar y exportar maquinarias, insumos y repuestos requeridos para el desarrollo de sus actividades; tomar dinero en prestamo, financiar y garantizar las operaciones comerciales que celebre con terceros relativas a su objeto; celebrar y ejecutar todo tipo de actos y contratos necesarios para desarrollar sus operaciones; girar, aceptar, otorgar y protestar todo tipo de titulos valores e instrumentos negociables; comprar, vender y constituir gravámenes sobre bienes muebles e inmuebles; designar representantes o apoderados en el pais y en el exterior y, en

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2009/06/19

HORA: 13:11:00

OPERACION: 10ERP0619107

PAGINA: 3

general, realizar cualquier acto o negocio que sea necesario o conveniente para el desarrollo de su objeto social y para la mejor proteccion de sus intereses corporativos o lo de sus socios.

CERTIFICA

Nro Acciones

Valor Accion

Autorizado

\$\*\*\*\*\*4,000,000,000 \*\*\*\*\*4,000,000 \*\*\*\*\*1,000

Suscrito

\$\*\*\*\*\*2,672,646,000 \*\*\*\*\*2,672,646 \*\*\*\*\*1,000

Pagado

\$\*\*\*\*\*2,672,646,000 \*\*\*\*\*2,672,646 \*\*\*\*\*1,000

CERTIFICA

ADMINISTRACION: Segun funciones de la junta directiva, entre otras:

Autorizar cualquier acto o contrato cuya cuantia sea superior al equivalente en pesos Colombianos a cincuenta mil dolares de los Estados Unidos de America (US\$50.000.00), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion y para enajenar o gravar bienes inmuebles y demas activos fijos de la sociedad, cualquiera que sea la cuantia de la transaccion. Las demas que le sean propias y no esten atribuidas a otro organo social y las que le correspondan en virtud de la ley. la sociedad tendra un Gerente General, quien ejercera la administracion y representacion legal de la sociedad y tendra las siguientes atribuciones, entre otras: Ejercer la representacion legal de la sociedad en todos los actos y contratos que se requieran para el desarrollo del objeto social, de conformidad con lo previsto en las leyes y en los presentes estatutos. Aprobar y celebrar en nombre de la sociedad todo acto o contrato cuya cuantia sea igual o inferior al equivalente en pesos Colombianos a cincuenta mil dolares de los Estados Unidos de America (US\$50.000.00), liquidados a la tasa de cambio representativa del mercado vigente el dia en que se surta la aprobacion o celebracion del acto. Para enajenar, a cualquier titulo, bienes inmuebles de la sociedad o constituir gravámenes sobre los mismos, debera obtener la aprobacion de la junta directiva, cualquiera que sea la cuantia de la transaccion; o las demas funciones que le corres-

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PREMIO  
COLOMBIANO  
A LA CALIDAD  
DE LA GESTION

ENTREGADO POR GRAMADIA S.A. NIT. 900.012.111-5 10064 01-2009

**CERTIFICADO NACIONAL**

**CÁMARA DE COMERCIO DE BARRANQUILLA**

FECHA: 2009/06/19

HORA: 13:11:00

OPERACION: 10ERP0619107

PAGINA: 4

pondan como representante legal por disposicion de la ley, de estos estatutos o de la junta directiva. El Gerente General tendra un suplente, designado por la junta directiva, quien lo reemplazara con identicas facultades en sus faltas temporales, absolutas o meramente accidentales, sin que sea necesario para ello acreditar la ausencia del principal.

**C E R T I F I C A**

Que según Acta No. 15 del 18 de Febrero de 2008 correspondiente a la Asamblea de Accionistas en Bogotá de la sociedad:

**GYNOPHARM S.A.**

cuya parte pertinente se inscribió en esta Cámara de Comercio, el 25 de Febrero de 2008 bajo el No. 919 del libro respectivo, fueron hechos los siguientes nombramientos:

**CLASE: JUNTA DIRECTIVA**

**Principales**

- |                                |                    |
|--------------------------------|--------------------|
| 1. Llobet Poal Manuel          | CC.*****14.670.196 |
| 2. Zanatta Rehernan Leonardo   | CC.*****2.760.271  |
| 3. Muñoz Marroquin Diego       | CC.*****7.688.292  |
| 4. Montealegre Gonzalez Andrés | CC.*****79.950.262 |

**Suplentes**

- |                                   |                    |
|-----------------------------------|--------------------|
| 1. Agudelo Pelaez Luis Hernando   | CC.*****14.238.997 |
| 2. Aroca Almanza Arleth Ayelina   | CC.*****36.718.415 |
| 3. Penaranda Urbina Adriana Paola | CC.*****53.120.683 |
| 4. Eovar Vasquez Ruth             | CC.*****52.175.736 |

**C E R T I F I C A**

Que según Acta No. 18 del 30 de Octubre de 2003 correspondiente a la Junta Directiva en Barranquilla de la sociedad: **GYNOPHARM S.A.**

cuya parte pertinente se inscribió en esta Cámara de Comercio, el 06 de Nov/bre de 2003 bajo el No. 107,783 del libro respectivo, fueron hechos los siguientes nombramientos:

|                              |                       |
|------------------------------|-----------------------|
| <b>Cargo/Nombre</b>          | <b>Identificación</b> |
| <b>Gerente General</b>       |                       |
| Palacios Aragon Luis Alberto | CE.*****319.788       |

**C E R T I F I C A**

Que según Acta No. 49 del 03 de Marzo de 2008 correspondiente a la

\*\*\* CONTINUA \*\*\*



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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2009/06/19 HORA: 13:11:00

OPERACION: 10ERP0619107

PAGINA: 5

Junta Directiva en Barranquilla, de la sociedad: GYNOPHARM S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 11 de Marzo de 2008 bajo el No. 138,342 del libro respectivo, fueron hechos los siguientes nombramientos:

| Cargo/Nombre                        | Identificación  |
|-------------------------------------|-----------------|
| Suplente del Gerente.               |                 |
| Mollajoli Centurion Andres Fernando | CE.*****351,283 |

CERTIFICA

Que según Acta No. 19 del 30 de Abril de 2009 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: GYNOPHARM S.A. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 27 de Mayo de 2009 bajo el No. 149,314 del libro respectivo, fueron hechos los siguientes nombramientos:

| Cargo/Nombre                        | Identificación      |
|-------------------------------------|---------------------|
| Revisor Fiscal.                     |                     |
| PENALOSA AUDITORES & ASOCIADOS S.A. | Ni.*****830,095,635 |

CERTIFICA

Que por Documento Privado del 11 de Mayo de 2009, otorgado en Bogotá por Peñalosa Auditores & Asociados S.A. inscrito en esta Cámara de Comercio, el 27 de Mayo de 2009 bajo el Nro 149,315 del libro respectivo, fueron hechos los siguientes nombramientos:

| Cargo/Nombre                       | Identificación     |
|------------------------------------|--------------------|
| Designado: Revisor Fiscal Ppal     |                    |
| Padilla Romero Ivan Dario          | CC.*****80,025,798 |
| Designado: Revisor Fiscal Suplente |                    |
| Gomez Preciado Clara Judith        | CC.*****52,544,226 |

CERTIFICA

Que según Documento Privado de fecha 10 de Octubre del 2.000, inscrito en esta Camara de Comercio el 23 de Noviembre del 2.000 bajo el No. 1.872 del libro repectivo, consta que el señor RUBEN MINSKI GONTOVNIK C.C. No. 7.463.982, actuando como Presidente y representante legal de la sociedad GYNOPHARM S.A., otorga Poder Especial, Amplio y Suficiente a KAREN JENNIFER FIGUEROA GARCIA C.C. No. 32.732.070, para que en nombre y representacion de la sociedad suscriba todas las declaraciones cambiarias a que esta obligada GYNOPHARM

\*\*\* CONTINUA \*\*\*

P R E M I O  
COLOMBIANO  
A LA CALIDAD  
DE LA GESTIÓN

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2009/06/19

HORA: 13:11:00

OPERACION: 10ERP0619107

PAGINA: 6

S.A., en el giro normal de sus negocios y operaciones sociales.-----

CERTIFICA

Que según Documento Privado de Fecha 10 de Octubre del 2.000, inscrito en esta Cámara de Comercio el 12 de junio del 2.002, bajo el 2.164 del libro respectivo, consta que el señor JORGE CASTELLANOS MARTINEZ, identificado con C.C.No.19.460.089, actuando como representante legal de la sociedad GYNOPHARM S.A, otorga Poder Especial Amplio y Suficiente a KAREN FIGUEROA GARCIA, identificada con la cedula de ciudadanía No.32.732.070 de Barranquilla, mediante documento privado de octubre 10/2000, inscrito en la Cámara de Comercio de Barranquilla bajo el No. 1.872 del libro respectivo, para que en representación de GYNOPHARM S.A, suscriba las declaraciones cambiarias a los que esta obligada GYNOPHARM S.A. en el giro ordinario de sus negocios y operaciones sociales.-----

CERTIFICA

Que en esta Cámara de Comercio no aparecen inscripciones posteriores de documentos referentes a reforma, disolución, liquidación o nombramientos de representantes legales de la expresada sociedad.-----

CERTIFICA

Que su última Renovación fue el: 31 de Marzo de 2009.  
La información sobre embargos de establecimiento se suministra en Certificados de Matrícula, la de contratos sujetos a registro, en Certificados Especiales.-----

CERTIFICA

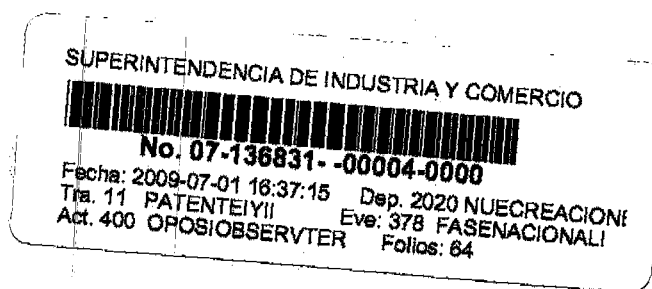
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*[Handwritten signature]*

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800178089-2

RECIBO OFICIAL DE CAJA : 09 - 47,645  
FECHA : JULIO 1 DE 2009



\*\*\*\*\* CONSIGNACION \*\*\*\*\*

| DEPOSITANTE   | TIPO PAGO    | BANCO           | CUENTA    | No. PAGO  | FECHA PAGO | Vr. PAGO     |
|---------------|--------------|-----------------|-----------|-----------|------------|--------------|
| GYNOFARM S.A. | CONSIGNACION | BANCO DE BOGOTA | 062754387 | 114281053 | 18/06/2009 | 4,305,000.00 |
| GYNOFARM S.A. | CONSIGNACION | BANCO DE BOGOTA | 062754387 | 114645996 | 27/03/2009 | 1,722,000.00 |

\*\*\*\*\* CONCEPTO \*\*\*\*\*

| CANT. RENTISTICO                            | CONCEPTO                      | TOTAL CONCEPTO |
|---------------------------------------------|-------------------------------|----------------|
| 1 50005-01-04 PRESENTACION DE OBSERVACIONES | 12 MARCAS Y LEMAS COMERCIALES | 287,000.00     |
|                                             | TOTAL :                       | \$ 287,000.00  |

SON: DOSCIENTOS OCHENTA Y SIETE MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No.

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                         |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|
| <b>(51) International Patent Classification<sup>7</sup>:</b><br><b>A61K 31/415, 9/20, 9/48, 9/50, 9/00</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | <b>A1</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | <b>(11) International Publication Number:</b> <b>WO 00/33835</b><br><b>(43) International Publication Date:</b> 15 June 2000 (15.06.00) |
| <b>(21) International Application Number:</b> PCT/EP99/10454<br><b>(22) International Filing Date:</b> 1 December 1999 (01.12.99)<br><b>(30) Priority Data:</b><br>98403037.9 4 December 1998 (04.12.98) EP<br><b>(71) Applicant (for all designated States except US):</b><br>SANOFI-SYNTHELABO [FR/FR]; 174, avenue de France, F-75013 Paris (FR).<br><b>(72) Inventors; and</b><br><b>(75) Inventors/Applicants (for US only):</b> ALAUX, Gérard [FR/FR]; 33, rue du Roussillon, Val des Quatre Pignons, F-78650 Beynes (FR). LEWIS, Gareth [GB/FR]; 39, avenue de Paris, F-91410 Dourdan (FR). ANDRE, Frédéric [FR/FR]; 14 bis du Clos de Massy, F-92160 Antony (FR).<br><b>(74) Agent:</b> THOURET-LEMAITRE, Elisabeth; Sanofi-Synthelabo, 174, avenue de France, F-75013 Paris (FR). | <b>(81) Designated States:</b> AE, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).<br><br><b>Published</b><br><i>With international search report.</i><br><i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> |                                                                                                                                         |
| <b>(54) Title:</b> CONTROLLED-RELEASE DOSAGE FORMS COMPRISING ZOLPIDEM OR A SALT THEREOF<br><br><b>(57) Abstract</b><br><br>The present invention relates to controlled-release dosage forms of zolpidem or salts thereof adapted to release zolpidem over a predetermined time period, according to a biphasic profile of dissolution, where the first phase is an immediate release phase and the second phase is a prolonged release phase and particular embodiments thereof intended to avoid abuse.                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                         |

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CONTROLLED-RELEASE DOSAGE FORMS COMPRISING ZOLPIDEM OR A  
SALT THEREOF

The present invention relates to controlled-release dosage  
5 forms comprising zolpidem or salts thereof.

EP 173 928 discloses an oral pharmaceutical controlled  
release preparation which has a biphasic release profile of  
a pharmacologically active agent, comprising a core  
10 containing the active agent and a coating applied thereon,  
wherein the coating consists of a film-forming polymer  
which is insoluble in water and gastro-intestinal fluids  
and a water-soluble pore-creating material also including  
the active agent.

15 EP 361 910 discloses granules which have a spray-dried  
substance carrying an adsorbed pharmaceutical and a layer  
comprising a pharmaceutically acceptable excipient and a  
pharmaceutical.

20 GB 2 245 492 discloses an orally administrable programmed  
release (i.e. release after a predetermined delay)  
pharmaceutical preparation comprising a core coated with a  
hydrophobic material and a surfactant.

25 Zolpidem is a suitable short acting hypnotic for the  
controlled-release dosage form according to the present  
invention. Zolpidem is a hypnotic from the therapeutical  
class of imidazopyridines. It is administrated orally by  
30 means of a tablet or other solid dosage form.  
Zolpidem acts rapidly. Indeed pharmacokinetic and  
pharmacodynamic data show that zolpidem has both a rapid  
absorption and onset of hypnotic action. Its  
bioavailability is 70% following oral administration and  
35 demonstrates linear kinetics in the therapeutical dose  
range, which lies between 5 and 10 mg in conventional  
forms, peak plasma concentration is reached at between 0.5  
and 3 hours, the elimination half-life is short, with a  
mean of 2.4 hours and a duration of action of up to 6

hours.

For reasons of simplicity, in the absence of contrary indication, within the whole description "zolpidem" or the "drug" means zolpidem per se as well as its salts.

5 The preferred salt of zolpidem is zolpidem hemitartrate.

Up to now, according to the rapidity of action of zolpidem, only immediate release dosage forms were developed, which disintegrate rapidly in the gastro-intestinal tract,  
10 dissolve in the fluid of the gastrointestinal tract and undergo systemic absorption, where zolpidem, can exert its pharmacological effect and induce sleep of the patient.

The new dosage forms according to the present invention  
15 enable to sustain release over a period compatible with the desired time of sleep and the time needed for elimination of the drug from the human body to a sufficiently low level.

20 Therefore, as a first object, the present invention provides controlled-release dosage forms comprising zolpidem or salts thereof adapted to release over a predetermined time period, according to a biphasic profile of dissolution, where the first phase is an immediate  
25 release phase and the second phase is a prolonged release phase.

The "total amount of drug" means the quantity by weight of the drug comprised in the whole dosage form according to  
30 the invention.

The first phase or immediate release phase is that part of the dissolution profile from 0 to 30 minutes in a suitable in vitro dissolution test. A suitable dissolution test is  
35 for example one of the method described in example 1: method where measurement is carried out in a type II dissolution apparatus according to U.S. pharmacopoeia in aqueous buffer at 37°C, or variations on this as well known to one who is skilled in the art. The proportion of the

drug dissolved during this phase is the proportion of the total amount of the drug which is dissolved at 30 minutes. In an advantageous embodiment of the dosage forms according to the present invention 90% or more of that part of the drug allotted for the first phase is dissolved in 20 minutes and more preferably in 15 minutes.

The second phase or prolonged release phase is that part of the dissolution profile which is after 30 minutes, measured in a suitable in vitro dissolution test, such as described in example 1. The present invention then proposes dosage forms of the drug whose complete dissolution time for the second phase is between 2 and 6 hours, and preferably between 2.25 and 3.5 hours.

The profile of the second, prolonged release phase is defined by the percentage released at times  $T_1$ ,  $T_2$ , and  $T_3$ , defined as follows.

$T_1$  is the beginning of the second phase of drug release, and is equal to 30 minutes.

$T_3$  is near the end of the second phase of drug release, and is the time at which 85% of the drug allotted for the second phase is released.

$T_2$  is the time at which 50% of the drug allotted for the second phase is released. For example, if 50% of the total amount of drug is released at 30 minutes, there is 50% remaining for the second phase of release.  $T_3$  is therefore the time for 92.5% dissolution [ $50\% + 0.85 \times 50\%$ ], and  $T_2$  is the time for 75% dissolution.

The second phase can represent a profile of release proportional to the square root of time, according to the equation proposed by T.Higuchi, *J.Pharm.Sci.* 52, 1145 (1963), sometimes called matrix release, where  $(T_2 - T_1) = 0.35(T_3 - T_1)$ . More advantageously the second phase can be first-order release where  $(T_2 - T_1) = 0.37(T_3 - T_1)$ . Still more advantageously the second phase can represent a profile of order zero or a sigmoidal profile. A profile of order zero is one where the release rate is constant or

near-constant, and  $(T_2 - T_1) = 0.59(T_3 - T_1)$ . A sigmoidal profile is one where the release rate in the second phase accelerates so  $(T_2 - T_1) > 0.59(T_3 - T_1)$ . Profiles intermediate between these different types are also covered.

The rapid release in the first phase induces the immediate sleep of the patient and the second phase allows the drug blood level to be maintained at or below the peak level, but higher than the level obtained with an immediate release dosage form, at the same time after dosing, with the objective of maintaining sleep.

The present invention then proposes dosage forms of zolpidem or a salt thereof whose complete dissolution time, defined as the time for release of 90% of the total amount of drug is between 2 and 6 hours and preferably between 2.25 and 3.5 hours.

40 to 70% of the total amount of drug can be released during the immediate release phase, preferably between 50 and 60%.

An example of such an *in vitro* release profile is given in figure 1, where 60% of the total amount of drug is released during the immediate release phase, and the second phase is zero order with 90% of the total amount of drug dissolved in 3 hours. Further examples of such profiles are shown in figure 2, where 50% of the total amount of drug is dissolved during the immediate release phase, and the second phase release is according to three other types of profile; release proportional to square root of time (matrix release), first order release, and a sigmoidal release profile.

35

As a second object, the present invention provides controlled-release dosage forms of zolpidem or salts thereof, characterised in that they comprise two kinds of pharmaceutical entities of drug: one immediate release

entity and one prolonged release entity. The drug dissolved during the immediate release phase (before 30 minutes) is contained within the immediate release entity, and that liberated in the prolonged release phase (after 30 minutes) is contained within the prolonged release entity.

Small quantities of the drug in a formulation for rapid release can be retained in the formulation and thus may be released at a time after 30 minutes from the beginning of the dissolution, and are thus included in the prolonged release phase. Similarly, small quantities of the drug incorporated in the prolonged release pharmaceutical entity may be released before 30 minutes, and thus form part of the immediate release phase.

According to the present invention, the proportion of the drug contained within the immediate release entity and dissolved within 30 minutes is at least 90%. And the proportion of the drug contained within the prolonged release entity and released within 30 minutes is comprised between 0 and 35%, and preferably between 0 and 25%.

Among dosage forms able to match the requirement of a biphasic profile and to comprise the two kinds of pharmaceutical entities defined above, the following may be cited: capsules, tablets, multilayer tablets, multicoated tablets.

The immediate release entity shall be understood in the present invention as a single pharmaceutical immediate release unit like for example an immediate release tablet or pellet, or several such units formulated into a capsule or a tablet ; as an immediate release matrix in a tablet ; as an immediate release layer, that can be incorporated in a multilayer tablet ; as an immediate release coating layer in a multicoated tablet or pellet.

The prolonged release entity shall be understood in the present invention as a pharmaceutical prolonged release unit such as, for example, a prolonged release tablet or

pellet, or several such units formulated into a capsule or a tablet; as a prolonged release layer, that can be incorporated in a multilayer tablet; as a prolonged release core or a prolonged release coating layer in a multicoated tablet; as prolonged release pellets within a disintegrating tablet.

Dosage forms where the immediate release entity and the prolonged release entity are administered simultaneously but separately are also encompassed in the present invention.

#### List of figures:

Figure 1 shows an example of a *in vitro* biphasic release profile, where the immediate release phase is 60% of the total amount of zolpidem, and the second phase is zero order with 90% of the total amount of zolpidem dissolved in 3 hours.

Figure 2 shows an examples of biphasic *in vitro* release profiles, where 50% is dissolved in the first phase, and the second phase release is (i) proportional to the square route of time (continuous line), (ii) first order (dotted line), and (iii) a sigmoid release profile (dashed line).

Figure 3 shows an *in vitro* dissolution profile of the tablets of example 1, in 0.01 M hydrochloric acid and in pH 6.8 phosphate buffer, as described in example 1.

Figure 4 shows an *in vitro* dissolution profile of the tablets of comparative example 1, in 0.01 M hydrochloric acid and in pH 6.8 phosphate buffer, as described in comparative example 1.

Figure 5 shows the results of a single dose pharmacokinetic study comparing the immediate tablet formulation of example 2 and the combination of an immediate release tablet and a prolonged release tablet of example 3.

Figure 6 shows the dissolution profile of a mixture of immediate release and prolonged release spheroids of example 4, in 0.01 M hydrochloric acid.

- 5 Figure 7 shows bilayer and multilayer tablets. (a) Bilayer tablet consisting of one immediate release layer and one prolonged release layer. (b) Triple layer tablet consisting of two outer immediate release layers and one inner prolonged release layer. (c) Triple layer tablets
- 10 consisting of an outer immediate release layer, an inner prolonged release layer, and an outer layer not containing active substance, modulating the release profile. (d) Triple layer tablets consisting of an outer immediate release layer, an outer prolonged release layer, and an
- 15 inner layer not containing active substance, modulating the release profile.

Figure 8 shows the dissolution profile of the bilayer tablet of example 6, in 0.01 M hydrochloric acid, and in pH

20 6.8 and pH 7.5 phosphate buffers.

Figure 9 shows the dissolution profiles of the bilayer tablet and of the combination of an immediate release and a prolonged release tablet of comparative example 2, in

25 0.01 M hydrochloric acid.

Figure 10 shows the dissolution profile of the bilayer tablet of comparative example 3, in 0.01 M hydrochloric acid and in pH 6.8 phosphate buffer.

30

Figure 11 shows the dissolution profile of the bilayer tablet of example 8, in 0.01 M hydrochloric acid.

The dosage forms according to the invention typically

35 contain from 4 to 16 mg of zolpidem as zolpidem base, and preferably 6 to 12 mg of zolpidem as zolpidem base. The zolpidem may be incorporated as the base, or as a pharmaceutically acceptable salt of zolpidem. Among dosage forms comprising a salt of zolpidem rather than the

zolpidem base, according to the invention, those comprising zolpidem hemitartrate are especially preferred.

In advantageous embodiments, dosage forms may be formulated  
5 in order to obtain in the second phase a dissolution independent of the pH. The preferred manner to achieve such a dissolution, in the case of basic drugs like zolpidem is to add a pharmaceutically acceptable organic acid into the dosage form, according to methods known from one skilled in  
10 the art. Such dosage forms are preferred.

These pharmaceutically acceptable organic acid can be chosen for example among maleic, tartaric, malic, fumaric, lactic, citric, adipic or succinic acid and their acid  
15 salts where these exist, in the form of racemates or isomers, where these exist. According to the invention, acids particularly preferred are tartaric, fumaric, citric, and succinic and their acid salts.

Various formulations, not limiting the scope of the present  
20 invention, illustrating the invention are described hereafter:

(1) A capsule comprising one or more immediate release tablets and one or more prolonged release tablets:  
25 Immediate release tablets may be prepared by direct compression of mixtures of the drug or salts thereof with diluents, such as microcrystalline cellulose, mannitol, sorbitol, and lactose. Other functional excipients such as disintegrants and lubricants can be added. Choice of these  
30 functional excipients as well as diluent is well known to anyone skilled in the art. Alternatively tablets may be prepared by granulation with water of a mixture of the drug or salts thereof with suitable diluents, disintegrant and binding polymer ; calibration and drying of the granulate ;  
35 addition of a lubricant, followed by compression on a tableting machine. The methods used are those generally described in the pharmaceutical literature, see for example, B. B. Sheth, F. J. Bandelin and R. JF. Shangraw, Compressed Tablets, in Pharmaceutical Dosage Forms:

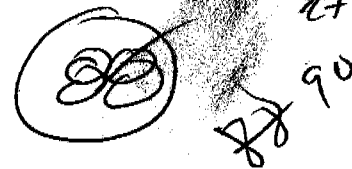
Tablets, Vol 1. edited by H. A. Lieberman and L. Lachman, Dekker N.Y. (1980).

Prolonged release tablets can be prepared by coating immediate release tablets with a diffusion limiting polymer coating. Suitable polymers can be chosen among ethyl cellulose, methyl methacrylate copolymers, such as Eudragit® RS, Eudragit® RL, Eudragit® NE commercialized by Röhm Pharma. Coating methods can consist in spraying a solution of the polymer on the tablets, either in a pan coater or a fluid bed coating apparatus. The solvent may be organic or aqueous, depending on the nature of the polymer used. Coating methods are described in the following works: J.M. Bakan, Microencapsulation, in L. Lachman, H. Lieberlman and J.L. Kanig (Eds.) The Theory and Practice of Industrial Pharmacy, Lea & Febinger, Philadelphia, USA, 1986 ; J.M. McGinity, Aqueous polymer coatings for Pharmaceutical Dosage Forms, Dekker NY, 1989. Alternatively prolonged release tablets can be prepared by incorporating matrix-forming excipients into the formulation, and omitting disintegrants. Such matrix-forming excipients may be hydrophilic polymers, which include hydroxypropylmethylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, and which swell in contact with aqueous liquids, and control release of the drug by diffusion through the swollen polymer network, and are incorporated at a level between 10 and 30% by weight with respect to that of the prolonged release tablet. Otherwise the matrix forming excipient may be a lipidic substance, such as hydrogenated castor oil, or carnuba wax, incorporated at a level between 10 and 40% by weight with respect to that of the prolonged release tablet. Prolonged release tablets can be formulated, as zolpidem is a basic drug optionnally with a pharmaceutically acceptable organic acid, chosen from the list given above so as to maintain the micro-pH of the tablet during dissolution in the neutral pH conditions of the small intestine.

(2) A capsule comprising a mixture of prolonged release

pellets and immediate release pellets:

- The immediate release pellets may be prepared by deposition of the drug suspended in water or an organic solvent such as ethanol with hydroxypropylmethylcellulose or povidone or another suitable polymer to act as a binder, onto a spherical granule. A fluid bed coating apparatus is generally used. Particles may be agglomerated to form spherical granules or pellets, in a high speed mixer granulator, or rotary fluid bed agglomerator. Those methods are described by K.W.Olson and A.M.Mehta, Int.J.Pharm.Tech&.Prod.Mfr. 6 18-24, 1985. Pellets may be also prepared by extrusion of wet masses or melts followed by spheronisation, for example as described in C. Vervact, L. Baert & J. P. Remon Int.J.Pharm. 116 (1995) 131-146.
- Excipients used are typically those with plastic qualities such as microcrystalline cellulose, but also mannitol. Small quantities of a polymeric binder are generally added. Surfactants such as sodium dodecyl sulphate may also be incorporated to give easier extrusion.
- Prolonged release pellets are prepared by coating immediate release pellets in the same way as described for the tablets. Coating may be carried out, for example, in coating pans or in fluid bed coater-driers. The amount and composition of the coating is adjusted from that used in the tablet, to reduce the permeability of the coating in order to take into account the far greater surface for diffusion in the pellets.
- Prolonged release pellets can, as zolpidem is a basic drug, contain a pharmaceutically acceptable organic acid so as to maintain the micro-pH of the interior of the pellet during dissolution in the neutral pH conditions of the small intestine.
- Alternatively, as zolpidem is a basic drug, prolonged release pellets may be coated with a pH sensitive membrane, containing polymers soluble at neutral pH and impermeable at acid pH, such as Eudragit® S, allowing increased permeation by the drug at pH 5 and above, to compensate for the decreased solubility of the drug at higher pH values.
- Alternatively sustained release pellets and immediate



release powder.

- (3) A tablet comprising a number of prolonged release coated pellets comprising the drug imbedded in a matrix also comprising the drug:  
Alternatively the tablet may consist of a mixture of prolonged release coated pellets and of immediate release non-coated pellets comprising the drug, imbedded in a drug-free matrix.
- 10 Alternatively the prolonged release coated pellets may be furthermore coated with a layer comprising the drug and other excipients allowing immediate release from that layer, imbedded in a drug-free matrix.
- The matrix surrounding the pellets should preferably be
- 15 formulated so that the compression into tablets does not interfere with the integrity of the membrane surrounding the pellets. On contact with fluid the tablet disintegrates, releasing the drug rapidly, from the matrix, or the immediate release pellets, or from the immediate
- 20 release pellet coating, and then releasing the drug from the prolonged release pellets slowly. The pellet may be formulated with a pharmaceutically acceptable organic acid so as to maintain the micro-pH of the pellet during dissolution in the neutral pH conditions of the small
- 25 intestine.

- (4) A multilayer tablet comprising:
- (i) one or two prolonged release layers, comprising the drug and a hydrophilic polymer (preferably a cellulose derivative),
- 30 (ii) one or more immediate release layers comprising the drug, and possibly,
- (iii) another layer not comprising the drug, but
- 35 comprising hydrophilic polymers, such as hydroxypropylcellulose, hydroxypropylcellulose, hydroxyethylcellulose or soluble diluents, such as lactose, sorbitol, mannitol, or hydrophilic polymers and soluble excipients, which layer modulates release

of the drug from the prolonged release layer. Each layer contains other excipients, so as to give suitable properties for compression, lubrication, binding as is well known to one skilled in the art. Examples of such bilayer and multilayer tablets are shown in figure 7a-d, where immediate release layers are designated by i, prolonged release layers by p and layers modulating the release profile by m.

- 10 (5) A multicoated tablet comprising:
- (i) a core comprising the drug and as zolpidem is a basic drugs, optionnally a pharmaceutically acceptable organic acid to maintain constant pH,
  - (ii) a polymer coating layer giving slow release of the
  - 15 drug from this core,
  - (iii) a coating layer comprising the drug which is released rapidly or immediately on contact of the dosage form with fluid.

Each portion of the tablet, in particular the inner core,

20 can contain other excipients, so as to give suitable properties for compression, lubrication, and binding as is well known to one skilled in the art. Methods for making both multilayered and multicoated tablets are described by W.C. Gunsel, Compression coated and layer tablets in

25 Pharmaceutical Dosage Forms: Tablets, Vol 1. edited by H. A. Lieberman and L. Lachman, Dekker N.Y. (1980).

As other particular embodiments encompassed within the scope of the present invention, pharmaceutical compositions

30 intended to avoid abuse may be cited.

Indeed it is known that some drugs and in particular hypnotics intended for legitimate oral use have the potential for abuse.

One way of substantially reducing or even eliminating this

35 potential for drug abuse for the pharmaceutical formulations that are objects of the present invention is to provide pharmaceutical compositions for oral administration comprising zolpidem capable at the same time of:

- liberating the active principle according to a biphasic in vitro profile as described above, following normal administration and,
- if it is introduced in a drink, whether or not containing alcohol, generating visual change or changes in the appearance of the drink. This visual change or changes are intended to avoid administration of the active principle to a person in the said drink without his or her knowledge.
- 10 These visual changes, according to the present invention include all means of indicating the presence of the said composition in a drink. The following may be cited as methods for inducing visual changes: inclusion of colouring excipients, floating of the composition at the surface of
- 15 the drink, formation of insoluble particles on the surface of the drink, on the brim of the glass, in the drink and/or on the bottom of the glass or a combination thereof. The drink, eventually with alcohol, may for example consist of coffee, tea, wine, fortified wine, spirits, liqueurs,
- 20 hot or cold chocolate-flavoured drinks, all gaseous alcoholic or not-alcoholic drinks, all cocktails or mixtures of fruit juice, milk, cream, ...

- Floating of the composition can be achieved by an
- 25 effervescence which can be obtained by means of a effervescence generator, as described hereinafter. In addition to these effervescent properties, the composition can present viscosity increasing properties appearing on contact with the drink. Thus when the bubbles
- 30 are formed, they are "trapped" and the composition swells. The lowering of the density contributes to maintaining the pharmaceutical composition at the surface of the drink. Such a viscosity may be obtained by one or more gelating substances. Hydrophilic excipients are particularly
- 35 suitable as gel-forming substances as set forth beneath.

Particles may be obtained by association of a lipophilic and a hydrophilic excipient, useful for the floating as described above. A list of suitable lipophilic excipients

is set forth beneath.

The composition according to this particular embodiment of the present invention can liberate particules even if the composition does not float or not immediately.

The effervescence generator can be a carbon dioxide generator system. It can comprise a suitable carbon dioxide generator agent and a pharmaceutically acceptable acid.

The carbon dioxide generator agent is normally a carbonate or bicarbonate of an alkali or alkaline earth metal or an amino acid. Calcium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, L-lysine carbonate, arginine carbonate or sodium sesquicarbonate may be cited as carbon dioxide generator agents.

The acid may be an acid anhydride, a monocarboxylic acid, a polycarboxylic acid or a partial salt of a polycarboxylic acid. More particularly citric, tartaric, ascorbic, fumaric, nicotinic, acetylsalicylic, maleic, adipic, succinic, malic, malonic acid may be chosen or glutaric anhydride, citric anhydride, monosodium citrate and succinic anhydride.

The carbon dioxide generator agent may be constituted by a mixture of carbon dioxide generating agents cited above.

In such a carbon dioxide generator system, the content of acidic compound is generally chosen such as the ratio between the number of moles in the said acidic compound with respect to the number of moles in the said carbon dioxide generator agent is between 1 and 2.

The gel forming substances can consist of one or more hydrophilic excipients provoking the swelling of the composition and the trapping of the gas released. In order to form insoluble particles, one or more lipophilic excipients are added to the hydrophilic excipient.

The process of effervescence and formation of particles

generate viscous agglomerates which float and stick to the glass. This process can last between 0.5 and 25 minutes depending on the type of drink.

- 5 Among lipophilic excipients the following may be cited:  
glycerol stearates, palmitostearates and behenates;  
hydrogenated vegetable oils and their derivatives;  
vegetable and animal wax and their derivatives;  
hydrogenated castor oils and their derivatives and cetylic  
10 esters and alcohols.

- Among hydrophilic excipients the following may be cited:  
cellulose derivatives, hydroxyethylcellulose,  
hydroxypropylcellulose (molecular mass from 50 to 1250  
15 kDa), hydroxypropylmethylcellulose (molecular mass from 10  
to 1500 kDa), carboxymethylcellulose and sodium  
carboxymethylcellulose; vegetable gums and their  
derivatives; derivatives of alginic acid;  
polyethyleneglycols and their derivatives; starches and  
their derivatives; silica, polymethacrylates and acrylic  
20 acid and methacrylate copolymers.
- One of the constituents of the gel forming substance can be  
chosen as being less soluble in alcohol.

- A colouring excipient can be advantageously added as giving  
25 rise to visual change preventing abuse. It can colour  
simultaneously the liquid or the particles or one  
independantly of the other.

- Among suitable colouring excipients the following may be  
cited : indigotine, cochineal carminic acid, yellow orange  
30 S, allura red AC, iron oxides, curcumin, riboflavin,  
tartrazine, quinoline yellow, azorubine, amaranth,  
carmines, erythrosine, red 2G, patented blue V, glittering  
blue FCF, chlorophylls, copper complexes of chlorophylls,  
green S, caramel, glittering black BN, carbo medicinalis  
35 vegetabilis, brown FK and HT, carotenoids, Annatto  
extracts, paprika extracts, lycopene, lutein,  
canthaxanthin, beetroot red, anthocyanes, calcium  
carbonate, titanium dioxide, aluminium, silver, gold or  
litholrubin BK or any other colouring excipient suitable

for an oral administration.

These visual means of preventing abuse may comprise a distinct pharmaceutical entity, not containing active substance, along with the immediate release and the sustained release entities, that comprise the pharmaceutical form, or they may be incorporated in one of these two entities. Yet a third method is to incorporate all or certain of them into a separate entity and at the same time add certain to the immediate or sustained release entity.

The method of incorporation of abuse resistance as described above will depend on the type of formulation. In the case of tablet formulations described above, including that of tablets enclosed inside a capsule, the abuse resistance conferring substances (colouring matter, effervescent couple...) may be included within the immediate release entity of the formulation.

Alternatively in the case of multilayer tablets and immediate tablets within a capsule they may be incorporated as a separate layer not containing active substance, but with the abuse resistance conferring substances. Such a layer may be added to the sustained release tablet or tablets within a capsule provided the said tablet is formulated as a matrix and is not coated with a coating conferring the sustained release properties.

In the case of a capsule containing controlled release pellets and immediate release pellets or granulate, abuse resistance conferring substances with the exception of an effervescent couple may be incorporated in the immediate release entity or added separately.

The examples which follow illustrate the invention without limiting it:

Example 1: prolonged release tablet comprising 10 mg zolpidem hemitartrate.

The first four of the following materials were mixed together, granulated with water, dried and calibrated. The granulate was then mixed with the magnesium stearate and compressed to a mass of 120 mg per tablet, using a rotary tableting machine.

|    |                                               |        |
|----|-----------------------------------------------|--------|
| 10 | zolpidem hemitartrate                         | 8.3 %  |
|    | lactose                                       | 86.6 % |
|    | citric acid                                   | 2.5 %  |
|    | hydroxypropylmethylcellulose 606 <sup>1</sup> | 2.1 %  |
|    | magnesium stearate                            | 0.5 %  |

<sup>1</sup> Pharmacoat 606, commercialized by Shin-Ensu Co

Tablets were coated, in an Accelacota pan coater, with a sufficient quantity of the following mixture to obtain the desired dissolution profile.

|    |                                  |        |
|----|----------------------------------|--------|
|    | ethylcellulose <sup>1</sup>      | 2.0 %  |
|    | diethylphthalate                 | 0.4 %  |
| 25 | hydroxypropylmethylcellulose 606 | 2.0 %  |
|    | isopropanol                      | 47.8 % |
|    | dichloromethane                  | 47.8 % |

<sup>1</sup> Ethocel, commercialized by Dow Chemical Co.

30

The *in vitro* dissolution profiles of the tablets were established using the Apparatus II of the United States Pharmacopoeia. Two dissolution media were employed: 900 ml hydrochloric acid 0.01 M and 900 ml of a pH 6.8 potassium phosphate 0.05 M buffer, maintained at  $37 \pm 0.5^\circ\text{C}$ . Stirring was by the paddle method (50 rpm). The percentage dissolved was determined by measurement of the UV absorbance at 270 nm (continuous sampling by a peristaltic pump in a closed system). The results are shown in figure 3.

Comparative example 1: prolonged release tablet without acid comprising 10 mg zolpidem hemitartrate.

- 5 Tablets were manufactured according to the same method as example 1, having the following composition:

|    |                                  |        |
|----|----------------------------------|--------|
|    | zolpidem hemitartrate            | 8.3 %  |
|    | lactose                          | 89.1 % |
| 10 | hydroxypropylmethylcellulose 606 | 2.1 %  |
|    | magnesium stearate               | 0.5 %  |

- They were coated with a polymer mixture comprising 50% hydroxypropylmethylcellulose and 50% ethylcellulose. Their in vitro dissolution profiles of the tablets were
- 15 established by the method of example 1.
- The results are shown in figure 4. They show that prolonged release tablets comprising acid present a profile of dissolution independent from the pH.

20

Example 2: Immediate release tablet comprising 10 mg zolpidem hemitartrate.

- Tablets dosed at 10 mg zolpidem hemitartrate and with
- 25 unitary mass 120 mg were manufactured according to the same method as example 1, having the following composition:

|    |                                            |        |
|----|--------------------------------------------|--------|
|    | zolpidem hemitartrate                      | 8.3 %  |
|    | lactose                                    | 75.8 % |
| 30 | microcrystalline cellulose <sup>1</sup>    | 10.0 % |
|    | hydroxypropylmethylcellulose 606           | 2.1 %  |
|    | sodium carboxymethylcellulose <sup>2</sup> | 3.2 %  |
|    | magnesium stearate                         | 0.6 %  |

- 35 <sup>1</sup> Avicel, commercialized by FMC
- <sup>2</sup> Primogel, commercialized by Avebe

The dissolution of the tablets was tested according to the method described in example 1, in the 0.01 M hydrochloric

40 acid medium. 90% of the amount of zolpidem contained in the

immediate release tablet were released in less than 30 minutes.

The obtained immediate release tablets were administered orally to 6 healthy volunteers in a pharmacokinetics study. Two tablets were administered orally to each volunteer in a single dose study. Blood samples were taken at 30 min, 1, 2, 3, 4, 6, 8, 10 hours, and analysed for zolpidem. The results (median zolpidem plasma levels) are plotted in figure 5 (closed squares).

Example 3: Pharmaceutical form consisting of an immediate release tablet comprising 10 mg zolpidem hemitartrate according to example 2, and a prolonged release tablet comprising 10 mg zolpidem hemitartrate according to example 1, within a gelatin capsule.

A pharmacokinetic study of a coadministration of a prolonged release tablet and a immediate release tablet was carried out. One immediate release tablet and one prolonged release tablet each comprising 10 mg zolpidem, as described above were administered to the same 6 volunteers as in the study described in example 2. The results (median zolpidem plasma levels) are plotted in figure 5 (open squares). The results show rapid increase in zolpidem levels to give a peak at 30 minutes, the same as for the immediate release, but plasma levels from 3-6 hours after dosing which are higher than those obtained with the same dose (20 mg) of the immediate release formulation. The whole quantity of zolpidem is released in a maximum time of about 8 hours. The dissolution profile was identical to that of the addition of the dissolution profiles of example 1 and 2. Thus the immediate and prolonged release pharmaceutical entities each contained 10 mg zolpidem hemitartrate (50%) and the immediate release phase was 12.2 mg (61%) and the prolonged release phase was 7.8 mg (39%). The complete dissolution time (90% released) was 2 h. The profile parameters are :  $T_3 = 2.12 \text{ h}$  ;  $T_2 = 1.19 \text{ h}$  ;  $(T_2 - T_1) = 0.43(T_3 - T_1)$ , the profile being close to zero-order.

Example 4: Capsule comprising a mixture of immediate release pellets and coated prolonged release pellets.

- 5 A suspension comprising 100 g zolpidem hemitartrate and 100 g povidone, commercialized under the reference Plasdone K29/32 by BASF, in 670 g ethanol was prepared. 750 g of this suspension was sprayed onto 1060 g of 16-18 mesh microgranules in a fluid bed drier. Dissolution of zolpidem
- 10 was tested in 0.01 M hydrochloric acid, according to the method in example 1. 80% was dissolved in 2 minutes, and 100% was dissolved at 30 minutes.
- A solution comprising 25 g of methacrylate copolymer Eudragit® RL100, 143 g of methacrylate copolymer
- 15 Eudragit® RS100 (both commercialized by Röhm Pharma) and 18.7 g of ethyl citrate commercialized under trademark Eudrafex® by Röhm Pharma as plasticiser, was prepared in 1180 g of a 60:40 m/m isopropanol/acetone mixture. Pellets comprising zolpidem were coated with this polymer mixture,
- 20 by spraying in a fluid bed dryer, the final amount of coating being 20% by mass of the uncoated pellet mass. After maturation of the pellets at 35°C for 24 hours, a mixture of these coated pellets and the uncoated pellets previously described was prepared in the proportion 1 : 1
- 25 by zolpidem content, and were filled into gelatin capsules to give a total amount of zolpidem hemitartrate content per capsule of 15 mg (12 mg zolpidem base). The dissolution of capsules was tested by the method of example 1, the resulting profile being shown in figure 6.
- 30 Thus the immediate and prolonged release pharmaceutical entities each contained 7.5 mg zolpidem hemitartrate (50%). Because of the lag-time of about 1h before release from the prolonged release entity, the immediate release phase (60%) and the prolonged release phase (40%) corresponded exactly
- 35 to the entities. The complete dissolution time (90% released) was 3.17 h. The profile parameters are :  $T_3 = 3.17 \text{ h}$  ;  $T_2 = 1.68 \text{ h}$  ;  $(T_2 - T_1) = 0.44(T_3 - T_1)$  and the profile was sigmoid in shape.

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Example 5: Tablet comprising coated prolonged release pellets comprising 5 mg zolpidem hemitartrate within a fast-disintegrating matrix comprising 7.5 mg zolpidem hemitartrate.

Prolonged release coated pellets were manufactured as described in example 4. The pellets were then spray-coated using the same method with a layer of 20% by mass of microcrystalline cellulose. A granule of the following composition was then prepared, by wet granulation:

|    |                                         |        |
|----|-----------------------------------------|--------|
|    | zolpidem hemitartrate                   | 8.4 %  |
|    | lactose                                 | 20.0 % |
| 15 | microcrystalline cellulose <sup>1</sup> | 62.9 % |
|    | hydroxypropylmethylcellulose 606        | 3.0 %  |
|    | crospovidone <sup>2</sup>               | 5.0 %  |
|    | magnesium stearate                      | 0.7 %  |

<sup>1</sup> Avicel, commercialized by FMC

<sup>2</sup> Kollidon CL, commercialized by BASF

This was mixed with the coated pellets in the proportion 3 parts of granulate to 2 parts of coated pellets (in terms of zolpidem content) and the mixture compressed into tablets dosed at 12.5 mg zolpidem hemitartrate (equivalent to 10 mg zolpidem base).

Example 6: Bilayer immediate/prolonged release tablet comprising 12.5 mg zolpidem hemitartrate.

Granulates were prepared by wet granulation according to the following compositions. The granulating process was that described in example 1 :

|    |                                 |        |
|----|---------------------------------|--------|
|    | GRANULATE 1 (Immediate release) |        |
|    | zolpidem hemitartrate           | 4.4 %  |
|    | lactose 150 mesh                | 68.3 % |
| 40 | microcrystalline cellulose      | 20.0 % |

|    |                                           |        |
|----|-------------------------------------------|--------|
|    | hydroxypropylmethylcellulose 606          | 2.5 %  |
|    | sodium carboxymethylcellulose             | 3.8 %  |
|    | magnesium stearate                        | 1.0 %  |
| 5  | GRANULATE 2 (prolonged release)           |        |
|    | zolpidem hemitartrate                     | 5.6 %  |
|    | lactose 150 mesh                          | 40.0 % |
|    | microcrystalline cellulose                | 20.0 % |
|    | tartaric acid                             | 8.4 %  |
| 10 | hydroxypropylmethylcellulose <sup>1</sup> | 25.0 % |
|    | magnesium stearate                        | 1.0 %  |

<sup>1</sup> Metolose 90SH4000, commercialized by Shin-Etsu

15 The mixtures were then compressed into bilayer tablets of the form shown in figure 7(a) using an alternative tablet press. Each tablet contained 12.5 mg zolpidem hemitartrate, the first immediate release layer with 125 mg of granulate 1 comprising 5.5 mg of zolpidem hemitartrate, and the

20 prolonged release layer with 125 mg granulate 2 comprising 7 mg zolpidem hemitartrate. The *in vitro* dissolution profiles of the tablets were established using the Apparatus 2 of the United States Pharmacopeia. Three

25 dissolution media were employed: hydrochloric acid 0.01 M, a pH 6.8 potassium phosphate 0.025 M buffer, and a pH 7.5 potassium phosphate 0.015 M buffer. The volume of dissolution medium was 500 ml, maintained at  $37 \pm 0.5^\circ\text{C}$ . Stirring was by the paddle method (75 rpm). A grill was

30 placed in the bottom of each vessel, to prevent sticking of the tablet to the glass surface. The percentage dissolved was determined by measurement of the UV absorbance at 310 nm (continuous sampling by a peristaltic pump in a closed system). The results are shown in figure 8. The

35 dissolution profile is almost independent of pH between pH 1 and 6.8. Zolpidem continues to be released at pH 7.5, though at a significantly reduced rate.

The immediate release entity contained 5.5 mg zolpidem hemitartrate (44%) and the prolonged release entity contained 7.5 mg zolpidem hemitartrate (56%). The complete

40 dissolution time (90% released) was 2.14 h. Because of release from the prolonged release pharmaceutical entity

from 0 to 0.5 h, the corresponding immediate release phase was 7.5 mg (60%) and the prolonged release phase was 5 mg (40%). The profile parameters are :  $T_3 = 2.23$  h ;  $T_2 = 1.38$  h ;  $(T_2 - T_1) = 0.51(T_3 - T_1)$ , the profile being zero-order.

Comparative example 2 : Comparison of the dissolution profile of a bilayer immediate/prolonged release tablet comprising 12.5 mg zolpidem hemitartrate with that of an immediate release and a prolonged release tablet of the same composition

Granulates were prepared by wet granulation according to the following compositions. The granulating process was that described in example 1:

|    |                                           |        |
|----|-------------------------------------------|--------|
|    | GRANULATE 1 (Immediate release)           |        |
|    | zolpidem hemitartrate                     | 6.0 %  |
| 20 | lactose 150 mesh                          | 66.7 % |
|    | microcrystalline cellulose                | 20.0 % |
|    | hydroxypropylmethylcellulose 606          | 2.5 %  |
|    | sodium carboxymethylcellulose             | 3.8 %  |
|    | magnesium stearate                        | 1.0 %  |
| 25 | GRANULATE 2 (prolonged release)           |        |
|    | zolpidem hemitartrate                     | 4.0 %  |
|    | lactose 150 mesh                          | 55.0 % |
|    | microcrystalline cellulose                | 20.0 % |
| 30 | hydroxypropylmethylcellulose <sup>1</sup> | 20.0 % |
|    | magnesium stearate                        | 1.0 %  |

<sup>1</sup> Metolose 90SH4000, commercialized by Shin-Etsu

A portion of each granulate was compressed into bilayer tablets of the form shown in figure 7(a) using an alternative tablet press. Each tablet contained 12.5 mg zolpidem hemitartrate, the first immediate release layer with 125 mg of granulate 1 comprising 6.5 mg of zolpidem hemitartrate, and the prolonged release layer with 125 mg granulate 2 comprising 6 mg zolpidem hemitartrate. The

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dissolution profile was tested using the Apparatus 2 of the United States Pharmacopeia. The dissolution medium was hydrochloric acid 0.01 M, maintained at  $37 \pm 0.5^\circ\text{C}$ . The volume was 500 ml and stirring was by the paddle method (75 rpm). The percentage dissolved was determined by measurement of the UV absorbance at 310 nm (continuous sampling by a peristaltic pump in a closed system). The results are shown in figure 9. The pH of the dissolution media had a marked affect on the profile, increased pH depressing the dissolution rate.

The remaining portions of each granulate of comparative example 2 were each compressed into tablets mass 125 mg, the immediate release tablet (granulate 1) comprising 7.5 mg zolpidem hemitartrate, and the prolonged release tablet comprising 5 mg zolpidem hemitartrate. The *in vitro* dissolution profiles of the tablets were established by the method of example 1.

The resulting profiles are shown on figure 9. Surprisingly, the presence of the immediate layer had a significant effect on the dissolution of the hydrophilic matrix prolonged release layer in the bilayer tablet, and whereas the dissolution profile of the separate tablets was the sum of the profiles of the separate tablets, the prolonged release phase of the bilayer tablet was considerably slower than in the case of the separate tablets.

Comparative example 3 : pH dependence of the dissolution profile of a bilayer tablet comprising 12.5 mg zolpidem hemitartrate without acid in the prolonged release layer

Granulates similar to those of example 6 were prepared, the only difference being that in the case of granulation 2 (prolonged release) the tartaric acid was missed out and replaced in the formulation by lactose (48.4%). The mixtures were then compressed into bilayer tablets of the form shown in figure 7(a) using an alternative tablet

press, as for example 6. The *in vitro* dissolution profiles of the tablets were established as for example 6, using two dissolution media : hydrochloric acid 0.01 M and pH 6.8 potassium phosphate 0.025 M buffer. The results are shown in figure 10. The dissolution profile in 0.01 M hydrochloric acid is very close to that of the formulation with acid (example 6), but the rate at pH 6.8 is much decreased.

Example 7: Three-layer immediate/prolonged release tablet comprising 12.5 mg zolpidem hemitartrate.

Granulates were prepared by the method of example 1 according to the following compositions:

LAYER 1 (immediate release)

|                                  |        |
|----------------------------------|--------|
| zolpidem hemitartrate            | 5.0 %  |
| lactose 150 mesh                 | 67.7 % |
| microcrystalline cellulose       | 20.0 % |
| hydroxypropylmethylcellulose 606 | 2.5 %  |
| sodium carboxymethylcellulose    | 3.8 %  |
| magnesium stearate               | 1.0 %  |

LAYER 2 (non-active)

|                            |        |
|----------------------------|--------|
| lactose (spray dried)      | 60.0 % |
| microcrystalline cellulose | 24.0 % |
| tartaric acid              | 10.0 % |
| hydroxyethylcellulose      | 5.0 %  |
| magnesium stearate         | 1.0 %  |

LAYER 3 (prolonged release)

|                                           |        |
|-------------------------------------------|--------|
| zolpidem hemitartrate                     | 6.0 %  |
| lactose 150 mesh                          | 40.0 % |
| microcrystalline cellulose                | 19.0 % |
| tartaric acid                             | 9.0 %  |
| hydroxypropylmethylcellulose <sup>1</sup> | 25.0 % |
| magnesium stearate                        | 1.0 %  |

<sup>1</sup> Metolose 90SH4000, commercialized by Shin-Etsu

They were compressed as described in example 6 into 3 layer tablets, of the form shown in figure 7(d) layer 1 comprising 100 mg of the granulate 1, with 5 mg zolpidem hemitartrate, layer 2 (the middle layer) comprising 100 mg of the granulate 2, and layer 3 comprising 125 mg of the granulate 3 and 7.5 mg zolpidem hemitartrate.

Example 8: Coated bilayer immediate/prolonged release tablet comprising 10 mg zolpidem hemitartrate and containing an efferevescent couple and a dye in the immediate release layer.

Mixtures were prepared according to the compositions shown below. The powder mixture 1 for the immediate layer was prepared by dry mixing of the first eight ingredients. the remaining three ingredients are than added. The granulate 2 for the prolonged release layer was prepared by granulation with water of the first five components, the reamining two components being mixed with the granulate after drying and sieving.

POWDER MIXTURE 1 (Immediate release)

|    |                               |        |
|----|-------------------------------|--------|
|    | zolpidem hemitartrate         | 3.6 %  |
| 25 | anhydrous lactose             | 11.3 % |
|    | microcrystalline cellulose    | 24.3 % |
|    | povidone K30                  | 5.0 %  |
|    | tartaric acid                 | 23.0 % |
|    | sodium bicarbonate            | 25.0 % |
| 30 | sodium carboxymethylcellulose | 3.0 %  |
|    | Indigotine W6004              | 0.8 %  |
|    | sodium dodecyl sulphate       | 2.0 %  |
|    | colloidal silica              | 1.0 %  |
|    | magnesium stearate            | 1.0 %  |

GRANULATE 2 (prolonged release)

|    |                                           |        |
|----|-------------------------------------------|--------|
|    | zolpidem hemitartrate                     | 4.4 %  |
|    | lactose 150 mesh                          | 36.0 % |
|    | tartaric acid                             | 8.4 %  |
| 40 | microcrystalline cellulose                | 20.0 % |
|    | hydroxypropylmethylcellulose <sup>1</sup> | 30.0 % |

|                    |       |
|--------------------|-------|
| colloidal silica   | 0.2 % |
| magnesium stearate | 1.0 % |

<sup>1</sup> Metolose 90SH4000, commercialized by Shin-Etsu

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The mixtures were then compressed into bilayer tablets of the form shown in figure 7(a) using a Manesty BL tablet press. Each tablet contained 10 mg zolpidem hemitartrate, the first immediate release layer with 125 mg of powder mixture 1 comprising 4.5 mg of zolpidem hemitartrate, and 10 the prolonged release layer with 125 mg granulate 2 comprising 5.5 mg zolpidem hemitartrate.

A film coating (4% with respect to tablet mass) of the 15 following composition, was applied as a 20% dispersion in absolute alcohol, using a coating turbine (Glatt GC300).

|                         |      |
|-------------------------|------|
| copovidone <sup>1</sup> | 12 % |
| ethylcellulose          | 12 % |
| 20 titanium dioxide     | 46 % |
| Talc                    | 30 % |

<sup>1</sup>Kollidon VA64, commercialized by BASF

25 The dissolution profile of the tablets was determined in 0.01M hydrochloric acid, using the apparatus and method described in example 6. The results are shown in figure 11.

Example 9: Coated trilayer immediate/prolonged release 30 tablet comprising 10 mg zolpidem hemitartrate and containing an effervescent couple and a dye.

Mixtures were prepared according to the compositions shown below. The powder mixture 1 for the immediate layer was 35 prepared by dry mixing of the first eight ingredients. the remaining three ingredients are then added. The granulate 2 for the prolonged release layer was prepared by granulation with water of the first five components, the remaining two components being mixed with the granulate after drying and 40 sieving.

|    |                                           |        |
|----|-------------------------------------------|--------|
|    | POWDER MIXTURE 1 (Immediate release)      |        |
|    | zolpidem hemitartrate                     | 4.0 %  |
|    | microcrystalline cellulose                | 36.4 % |
| 5  | povidone K30                              | 5.0 %  |
|    | tartaric acid                             | 23.0 % |
|    | sodium bicarbonate                        | 25.0 % |
|    | sodium carboxymethylcellulose             | 3.0 %  |
|    | black iron oxide                          | 0.3 %  |
| 10 | Indigotine                                | 0.8 %  |
|    | sodium dodecyl sulphate                   | 1.0 %  |
|    | colloidal silica                          | 1.0 %  |
|    | magnesium stearate                        | 0.5 %  |
| 15 | POWDER MIXTURE 2 (Anti-abuse)             |        |
|    | microcrystalline cellulose                | 40.4 % |
|    | povidone K30                              | 5.0 %  |
|    | tartaric acid                             | 23.0 % |
|    | sodium bicarbonate                        | 25.0 % |
| 20 | sodium carboxymethylcellulose             | 3.0 %  |
|    | black iron oxide                          | 0.3 %  |
|    | Indigotine                                | 0.8 %  |
|    | sodium dodecyl sulphate                   | 1.0 %  |
|    | colloidal silica                          | 1.0 %  |
| 25 | magnesium stearate                        | 0.5 %  |
|    | GRANULATE 3 (prolonged release)           |        |
|    | zolpidem hemitartrate                     | 4.0 %  |
|    | lactose 150 mesh                          | 36.0 % |
| 30 | tartaric acid                             | 8.4 %  |
|    | microcrystalline cellulose                | 20.4 % |
|    | hydroxypropylmethylcellulose <sup>1</sup> | 30.0 % |
|    | colloidal silica                          | 0.2 %  |
| 35 | magnesium stearate                        | 1.0 %  |

<sup>1</sup> Metolose 90SH4000, commercialized by Shin-Etsu

The mixtures were then compressed into trilayer tablets of the form shown in figure 7(d) - the layer not containing  
40 zolpidem, that is of granulate 2, being designated by m -  
using a Manesty BL tablet press. Each tablet contained 10  
mg zolpidem hemitartrate. Each layer comprised 125 mg  
granulate or powder mixture, and the immediate release and

## Claims

1. A pharmaceutical composition comprising zolpidem or a salt thereof characterised in that it consists of a controlled-release dosage form adapted to release zolpidem or its salt over a predetermined time period, according to a biphasic in vitro profile of dissolution when measured in a type II dissolution apparatus according to U.S. Pharmacopoeia in aqueous buffer at 37°C, where the first phase is an immediate release phase and the second phase is a prolonged release phase.
2. A pharmaceutical composition according to claim 1, characterized in that the first phase has a maximum duration of 30 minutes.
3. A pharmaceutical composition according to claim 1 or 2 characterized in that the second phase has a profile of zero order release.
4. A pharmaceutical composition according to claim 1 or 2 characterized in that the second phase has a profile where the release is proportional to the square root of the time.
5. A pharmaceutical composition according to claim 1 or 2 characterized in that the second phase has a profile of first order release.
6. A pharmaceutical composition according to claim 1 or 2 characterized in that the second phase has a sigmoidal release profile.
7. A pharmaceutical composition according to any one of claims 1 to 6 characterized in that 40 to 70% of the total amount of zolpidem is released during the immediate release phase.
8. A pharmaceutical composition according to any one of claims 1 to 7 characterized in that the time for release of

90% of the total amount of zolpidem is between 2 and 6 hours.

9. A pharmaceutical composition comprising zolpidem or a salt thereof characterized in that it comprises two kinds of pharmaceutical entities: one immediate release entity and one prolonged release entity.
10. A pharmaceutical composition according to claim 9 characterized in that it consists in a dosage form chosen among capsules, tablets, multilayer tablets, multicoated tablets.
11. A pharmaceutical composition according to claim 9 or 10 characterized in that it consists of a capsule comprising one or more immediate release tablets and one or more prolonged release tablets.
12. A pharmaceutical composition according to claim 9 or 10 characterized in that it consists of a capsule comprising a mixture of prolonged release pellets and immediate release pellets.
13. A pharmaceutical composition according to claim 9 or 10 characterized in that it consists of a tablet comprising a number of prolonged release coated pellets comprising the drug imbedded in a matrix also comprising the drug.
14. A pharmaceutical composition according to claim 9 or 10 characterized in that it consists of a multilayer tablet comprising:
- (i) one or two prolonged release layers, comprising the drug and a hydrophilic polymer (preferably a cellulose derivative),
  - (ii) one or more immediate release layers comprising the drug,
  - and possibly,
  - (iii) another layer not comprising the drug, but comprising hydrophilic polymers.

15. A pharmaceutical composition according to claim 9 or 10 characterized in that it consists of a multicoated tablet comprising:

- 5 (i) a core comprising the drug and optionnally a pharmaceutically acceptable organic acid to maintain constant pH,
- (ii) a polymer coating layer giving slow release of the drug from this core,
- 10 (iii) a coating layer comprising the drug which is released rapidly or immediately on contact of the dosage form with fluid.

16. A pharmaceutical composition according to claim 9 characterized in that the immediate release entity and the  
15 prolonged release entity are administered simultaneously but separately.

17. A pharmaceutical composition according to any one of claims 1 to 16 characterized in that the prolonged release  
20 entity comprises a pharmaceutically acceptable organic acid which can be chosen among tartaric, malic, fumaric, lactic, citric, adipic or succinic acid and their acid salts, in the form of racemates or isomers.

25 18. A pharmaceutical composition according to any one of claims 1 to 17 characterized in that it is capable of generating visual change if it is introduced into a drink, whether or not containing alcohol,

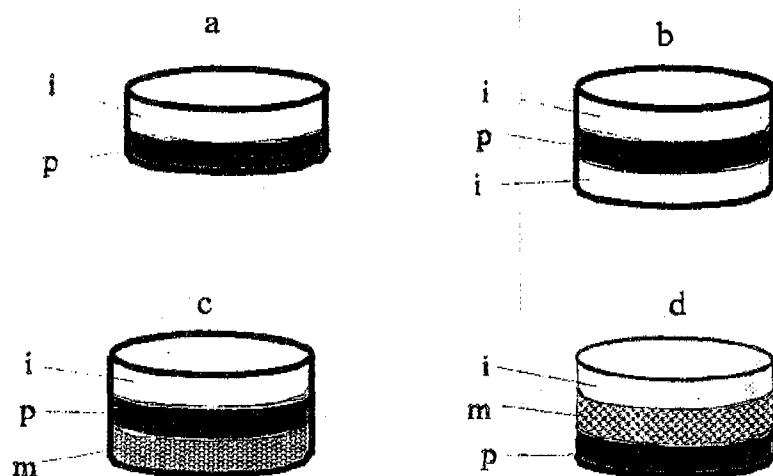
30 19. A pharmaceutical composition according to claim 18 characterized in that the visual change consists of release of included colouring excipients, or floating of the composition at the surface of the drink, or formation of insoluble particles on the surface of the drink, on the  
35 brim of the glass, in the drink and/or on the bottom of the glass or a combination thereof.

20. A pharmaceutical composition according to claim 19 characterized in that it comprises an effervescence

117

119-86

Figure 7



# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 99/10454

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/415 A61K9/20 A61K9/48 A61K9/50 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search

11 April 2000

Date of mailing of the international search report

18/04/2000

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# INTERNATIONAL SEARCH REPORT

International Application No

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