



No. 09-041709- -00004-0000

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Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 62

FORMULARIO ÚNICO DE OPOSICIÓN

①

OPOSICIÓN A:

- | | |
|--|--|
| ☒ Patente de Invención. | ☐ Marca Colectiva. |
| ☐ Patente de Modelo de Utilidad. | ☐ Marca de Certificación. |
| ☐ Diseño Industrial. | ☐ Lema Comercial. |
| ☐ Esquema de Trazado para Circuitos Integrados. | |
| ☐ Marcas de Productos o Servicios. | |

②

Numero del expediente: 09-041.709

Solicitante: HELSINN HEALTHCARE SA

SOLICITUD

PUBLICADA

Aboderado: EMILIO FERRERO

Título de la nueva creación o denominación del signo: CAPSULAS BLANDAS QUE
COMPRENDEN CLORHIDRATO DE PALONOSETRON QUE CONTIENEN ESTABILIDAD Y
BIODISPONIBILIDAD MEJORADA

Carla:

616

③

OPOSICIÓN PRESENTADA POR:

SOLICITANTE	Nombre: GYNOPHARM S.A.S.	IDENTIFICACIÓN	
	Dirección: Carrera 14 N° 94-44 Piso 7 Torre b	C.C. ☐	NIT ☒
	Nacionalidad o Domicilio: COLOMBIA	C.E. ☐	Otro ☐
	Lugar de Constitución: BARRANQUILLA	Cual _____	
	Teléfono: 2 36 84 95 Fax:	Número 802.006.279-4	
	E-mail:		
REPRESENTANTE O APODERADO	Nombre: ELIANA ISaura MORENO BOHORQUEZ	IDENTIFICACIÓN	
	Dirección: CARRERA 13 No. 119-95	C.C. ☒	NIT ☐
	Teléfono: (571)213 12 13 Fax: (571)612 19 79	C.E. ☐	Otro ☐
	E-mail: negocios@optimum-co.com	Cual _____	
		Número 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 demostrara 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.

⑦

NOMBRE: ELIANA ISAURA MORENO BOHORQUEZ

FIRMA: _____

C.C. 51'975.664

TP. 83823

Señora Jefe,
DIVISIÓN DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

Referencia : Expediente N° 09 041709
Asunto : Oposición a la solicitud de patente de Invención titulada
"CAPSULAS BLANDAS QUE COMPRENDEN
CLORHIDRATO DE PALONOSETRON QUE
CONTIENEN ESTABILIDAD Y BIODISPONIBILIDAD
MEJORADA"
Solicitante : HELSINN HEALTHCARE SA.
Opositora : GYNOPHARM S.A.S.

Publicada en la Gaceta de la Propiedad Industrial
N° 616 del 20 de mayo de 2010

Yo, *ELIANA ISAURA 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.S.* 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 "CAPSULAS BLANDAS QUE COMPRENDEN CLORHIDRATO DE PALONOSETRON QUE CONTIENEN ESTABILIDAD Y BIODISPONIBILIDAD MEJORADA", cuyos

titulares son HELSINN HEALTHCARE SA, 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 PALONOSETRON. 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 24 de abril de 2009 reivindicando prioridad bajo la solicitud US20060854342P del 2006-10-24; y fue publicada en Colombia, en la Gaceta de la Propiedad Industrial N° 616 del 20 de mayo de 2010, cuya publicación internacional corresponde a la WO2008049552 del 2008-05-02.

2.2. La solicitud colombiana 09 041709 objeto de la presente oposición, está dirigida a proveer una cápsula de gelatina blanda para administración oral que comprende

una cubierta exterior de gelatina blanda que tiene una permeabilidad al oxígeno de menos de aproximadamente 1.0×10^{-3} ml-cm/(cm²-24 hr. atm); y una composición de relleno interno líquido lipófila que comprende más de aproximadamente 50% en peso de uno o más componentes lipófilos; de aproximadamente 1 a aproximadamente 20% en peso de agua miscible u homogenizada en dichos uno o más componentes lipófilos; de aproximadamente 0.05 a aproximadamente 2.0 mg. de palonosetrón como clorhidrato de palonosetrón solubilizado o disperso en dicha agua; y un tensoactivo. En donde dicha cápsula exhibe las farmacocinéticas cuando se ingiere oralmente en un estado de ayuno que es bioequivalente a una formulación que tiene más de 95% de biodisponibilidad absoluta, en donde se establece bioequivalencia mediante un intervalo de confianza de 90% para AUC que está entre 80% y 125%.

2.3. Con base en el artículo 14 de la Decisión 486 de la CAN que consagra: *“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”*, tenemos que 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 afectan la patentabilidad de la presente solicitud:

- D1: WO2004045615 publicada el 03 de junio de 2003.
- D2: US2004052824 publicada el 18 de marzo de 2004.

2.4. Ahora bien, el documento D1, se revela palonosetrón en cápsulas que comprende un líquido (aceite graso) como portador para el tratamiento de la emesis. Dicho documento D1 revela adicionalmente un relleno interior que consta de una fase

continua que comprende palonosetrón lipófilo en una fase acuosa homogeneizada, formulación que según el mismo documento D1, resulta en una mayor estabilidad del agente activo en lo que respecta a la degradación (oxidación), así como en la biodisponibilidad mejorada.

2.5. El documento D2 por su parte se refiere a composiciones farmacéuticas capaces de comprender micelas que contienen al menos un principio altamente lipófilo, lo que permite aumentar la biodisponibilidad del principio activo insoluble en solventes acuosos llamada MIDDs (R), o Mejora de las soluciones de suministro micelar de Drogas (Micellar Improved Drug Delivery Solutions).

2.6. Tomando los documentos D1 y D2 como el estado del arte más cercano a la solicitud objeto de la presente oposición, aunque fuera posible reconocer novedad, no es posible reconocer altura inventiva, ya que sería obvio para un experto en la materia a partir del documento D1 por si solo o en combinación con D2, concebir una cápsula de gelatina blanda para administración oral que comprende una cubierta exterior de gelatina; y una composición de relleno interno líquido lipófila que comprende más de aproximadamente 50% en peso de uno o más componentes lipófilos; de aproximadamente 1 a aproximadamente 20% en peso de agua miscible u homogeneizada en dichos uno o más componentes lipófilos; de aproximadamente 0.05 a aproximadamente 2.0 mg. de palonosetrón como clorhidrato de palonosetrón solubilizado o disperso en dicha agua; y un tensoactivo, con estabilidad superior y bioestabilidad mejorada. Así entonces las reivindicaciones de la solicitud objeto de la presente oposición, carecen de altura inventiva.

2.7. En consecuencia y de acuerdo a lo descrito anteriormente, se deriva que la solicitud colombiana 09 041709 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.

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

2.8.1. CARENCIA DE ALTURA INVENTIVA. Según la Decisión 486 de la Comunidad Andina de Naciones, Artículo 18.- *"Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica."* A la fecha de prioridad, 24 de octubre de 2006, a partir del a partir del documento D1 por si solo o en combinación con D2, un experto en la materia puede llegar de manera evidente a una cápsula de gelatina blanda para administración oral que comprende una cubierta exterior de gelatina; y una composición de relleno interno líquido lipófila que comprende más de aproximadamente 50% en peso de uno o más componentes lipófilos; de aproximadamente 1 a aproximadamente 20% en peso de agua miscible u homogenizada en dichos uno o más componentes lipófilos; de aproximadamente 0.05 a aproximadamente 2.0 mg. de palonosetrón como clorhidrato de palonosetrón solubilizado o disperso en dicha agua; y un tensoactivo, con estabilidad superior y bioestabilidad mejorada; sobre lo cual busca protección en el capítulo reivindicatorio.

2.9. 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.

2.10. Por todo lo anterior, atentamente solicito a usted que se sirva declarar fundada la presente oposición y en consecuencia negar el registro a la solicitud de patente titulada “CAPSULAS BLANDAS QUE COMPRENDEN CLORHIDRATO DE PALONOSETRON QUE CONTIENEN ESTABILIDAD Y BIODISPONIBILIDAD MEJORADA”, cuyos titulares son HELSINN HEALTHCARE SA, solicitud Colombiana que apareció publicada en la Gaceta de la Propiedad Industrial N° 616 del 20 de mayo de 2010.

3. PRUEBAS

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

- D1: WO2004045615 publicada el 03 de junio de 2003.
- D2: US2004052824 publicada el 18 de marzo de 2004.

4. FUNDAMENTO DE DERECHO

Fundamento esta observación en las normas legales siguientes:

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

4.2. Artículo 42 de la Decisión 486 de la Comisión del Acuerdo de Cartagena.

4.3. En las demás normas concordantes.

5. ANEXOS

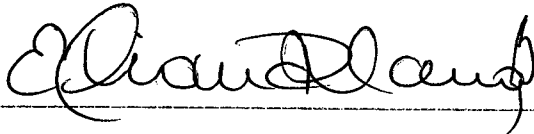
Para los efectos correspondientes anexo al presente escrito los siguientes documentos:

1. Poder para actuar en el presente.
2. Documento que acredita al representante legal de GYNOPHARM S.A.S.
3. Recibo de caja del respectivo pago de tasa.
4. Copias de los documentos:
 - D1: WO2004045615 publicada el 03 de junio de 2003.
 - D2: US2004052824 publicada el 18 de marzo de 2004.

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 ISAURA MORENO BOHORQUEZ
C.C. 51'975.664 de Bogotá
T.P.A. 83823 del C.S. de la J.

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.S.** 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. **09 041.709**, titulada "**CÁPSULAS BLANDAS QUE COMPRENEN CLORHIDRATO DE PALONOSETRON QUE TIENEN ESTABILIDAD Y BIODISPONIBILIDAD MEJORADA**", cuyo titular es **HELSINN HEALTHCARE S.A.**, publicada en la gaceta No. 616 del 20 de mayo de 2010.

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 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 2010.

GYNOPHARM S.A.S.

Cédula de Extranjería: No. 319788.

NIT: 802.006.279-4

Representante Legal

Acepto:

ELIANA ISAURA MORENO BOHÓRQUEZ

C.C. 51'975.664 de Bogotá

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





DILIGENCIA DE RECONOCIMIENTO

Compareció ante el Notario 18 del Círculo de Bogotá.

quien exhibió a C

E 31 9788

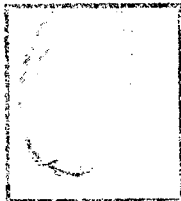
Expedida en y declaró que la firma y huella que aparecen en el presente documento son suyas y que el contenido del mismo es cierto.

06 AGO 2010

BOGOTÁ, D.C.

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Firma

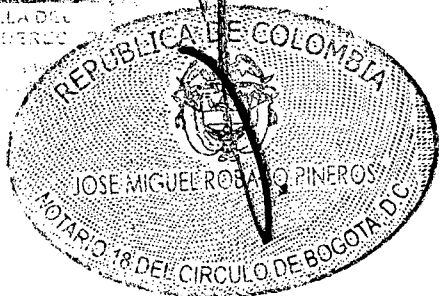


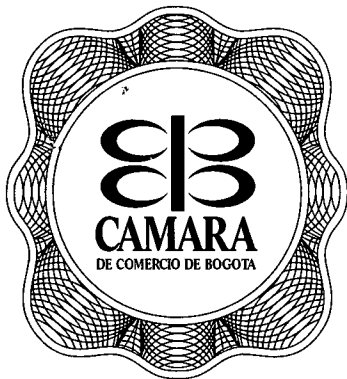
HUELLA DEL INDICADOR

EL NOTARIO

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NOTARIA DIECIOCHO DEL CÍRCULO DE BOGOTÁ D.C.
LA HUELLA SE AUTENTICA POR SOLICITUD DE INTERESADO





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12

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2010/08/10

HORA: 10:45:56

OPERACION: 03R050810087

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 según Acta No. 22 del 29 de Abril de 2010 correspondiente a la Asamblea de Accionistas en Barranquilla, inscrito(as) en esta Cámara de Comercio, el 24 de Junio de 2010 bajo el No. 160,098 del libro respectivo, la sociedad antes mencionada-----
se transformo en por acciones simplificada bajo la denominación de GYNOPHARM S.A.S.-----

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
22	2010/04/29	Asamblea de Accionistas en Ba	160,098	2010/06/24

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.S.-----

SIGLA: .

DOMICILIO PRINCIPAL: Barranquilla.

NIT No: 802.006.279-4.

MATRICULA MERCANTIL: 245,470.

C E R T I F I C A

Direccion para notificaciones judiciales:

CR 49 C No 80 - 125 OF 512.

*** CONTINUA ***

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2010/08/10

HORA: 10:45:56

OPERACION: 03R050810087

PAGINA: 2

De la ciudad de Barranquilla.

Correo electrónico: mvenegas@gynopharm.com.co

Pagina Web:

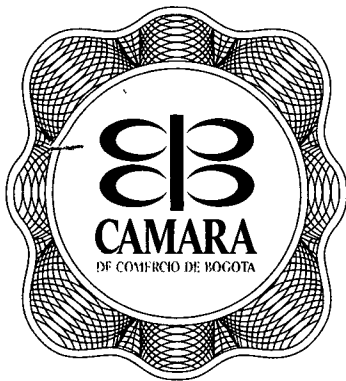
C E R T I F I C A

DURACION: El término de duración de la sociedad se fijó hasta el 16 de Dic/bre de 2087.

C E R T I F I C A

OBJETO SOCIAL: El objeto de la sociedad es el ejercicio de todas las actividades comerciales para: 1) La importacion, exportacion, fabricacion, comercializacion, distribucion y venta de productos farmaceuticos, higienicos, veterinarios e implementos medicos. 2) Cualquier otra actividad lícita de comercio relacionada con su objeto social principal y todo lo que se relaciona con la importacion de los bienes y equipos necesarios para el desarrollo de su objeto social. 3) Tener la representación en Colombia de empresas o sociedades establecidas fuera del territorio colombiano, cuyo objeto sea similar o complementario. En desarrollo de su objeto social principal, la sociedad podra adelantar y celebrar los siguientes actos y contratos: A) Exportar e importar, agenciar, distribuir, comercializar, comprar o vender a comision o consignacion o de cualquier otra forma o modalidad, toda clase de equipos, aparatos, bienes al por mayor o al detal, y servicios relacionados con su actividad. B) Gravar en cualquier forma los bienes de su propiedad muebles o inmuebles, dar en prenda los primeros o hipotecar los segundos para garantizar obligaciones de la sociedad. C) Constituir apoderados que le representen, asociarse con otras compañías de la misma o parecida naturaleza y en general realizar toda clase de operaciones comerciales o civiles y ejecutar o celebrar toda clase de contratos o actos del mismo orden, ya sean industriales, comerciales o financieros encaminados a alcanzar los fines que se proponen. D) Adquirir, enajenar, administrar, recibir o dar en arrendatario o a cualquier titulo, toda clase de bienes muebles e inmuebles. E) Intervenir ante terceros o ante los accionistas mismos como acreedora o como deudora en toda clase de operaciones de credito, dando o recibiendo las garantias del caso,

*** CONTINUA ***



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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2010/08/10

HORA: 10:45:56

OPERACION: 03R050810087

PAGINA: 3

cuando haya lugar a ellas; F)Efectuar cualquier clase de operaciones de credito activo o pasivo, tales como constituir depositos, efectuar prestamos. Otorgar o recibir documentos negociables, girar, aceptar, endosar, asegurar y negociar en general titulos valores recibirlos en pago; G)Celebrar y ejecutar en general todos los actos y contratos preparatorios, complementarios o accesorios de todos los anteriores, los que se relacionen con la existencia y funcionamiento de la sociedad, y los que sean conducentes al buen logro de los fines sociales.-----

C E R T I F I C A

CAPITAL

Nro Acciones

Valor Acción

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

C E R T I F I C A

ADMINISTRACION: La sociedad tendra los siguientes organos de direccion y administracion: Asamblea General de Accionistas. Junta Directiva. Gerencia, la cual sera asumida por un Gerente quien tendra representacion legal de la sociedad. Son funciones de la Asamblea General de Accionistas las siguientes entre otras: Nombrar al Gerente y fijar los honorarios a que tenga derecho; Autorizar al Gerente para adquirir, enajenar, recibir o dar en arrendamiento o a cualquier otro titulo, toda clase de bienes inmuebles de la sociedad o bienes muebles diferentes a los productos comercializados ordinariamente por la sociedad. Son funciones de la Junta Directiva las siguientes entre otras: Autorizar cualquier acto o contrato que pretenda suscribir el Gerente, que supere en cuantia el equivalente a 300 SMLMV(TRESCIENTOS SALARIOS MINIMOS MENSUALES LEGALES VIGENTES) debera obtener la autorizacion previa de la Junta Directiva. La sociedad tendra un Gerente quien sera elegido por Asamblea. El Gerente de la sociedad tiene a su cargo la administracion inmediata de la sociedad, asi como la representacion legal de la misma y en

*** CONTINUA ***

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2010/08/10

HORA: 10:45:56

OPERACION: 03R050810087

PAGINA: 4

tal virtud le estan asignadas las siguientes funciones y atribuciones entre otras: Llevar la representacion de la entidad, tanto judicial como extrajudicialmente. Constituir, para casos especiales, apoderados judiciales o extrajudiciales. Celebrar los actos, operaciones y contratos conducentes al buen logro del objeto de la sociedad. Cualquier acto o contrato que supere en cuantia el equivalente a 300 SMLMV (TRESCIENTOS SALARIOS MINIMOS MENSUALES LEGALES VIGENTES) debera obtener la autorizacion previa de la Junta Directiva.-----

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 Bogota, de la sociedad:

GYNOPHARM S.A.S.-----

cuya parte pertinente se inscribió en esta Cámara de Comercio, el 25 de Febrero de 2008 bajo el No. 137,919 del libro respectivo, fueron hechos los siguientes nombramientos:

CLASE:

JUNTA DIRECTIVA

Principales

- | | |
|---|--------------------|
| 1. Llobet Poal Manuel | CC.*****14,670,196 |
| 2. Zanatta Reheman Leonardo Andres | CC.*****2,760,271 |
| 3. Munoz Marroquin Diego | CC.*****7,688,292 |
| 4. Montealegre Gonzalez Andres Leonardo | 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. tovar Vasquez Ruth | CC.*****52,175,756 |

C E R T I F I C A

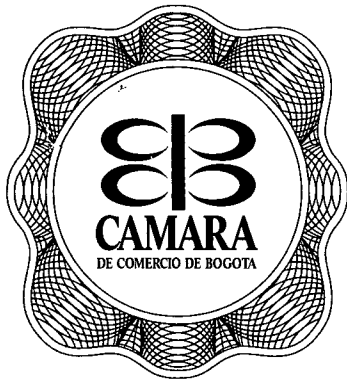
Que según Acta No. 18 del 30 de Octubre de 2003 correspondiente a la Junta Directiva en Barranquilla, de la sociedad: GYNOPHARM S.A.S. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 06 de Nov/bre de 2003 bajo el No. 107,783 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre

Identificación

Gerente General.

*** CONTINUA ***



01



* 9 5 5 1 4 1 5 0 *

14

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2010/08/10

HORA: 10:45:56

OPERACION: 03R050810087

PAGINA: 5

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 Junta Directiva en Barranquilla, de la sociedad: GYNOPHARM S.A.S. 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

C E R T I F I C A

Que según Acta No. 23 del 25 de Junio de 2010 correspondiente a la Asamblea de Accionistas en Barranquilla, de la sociedad: GYNOPHARM S.A.S. cuya parte pertinente se inscribió en esta Cámara de Comercio, el 14 de Julio de 2010 bajo el No. 160,520 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre

Identificación

Revisor Fiscal.

DELOITTE & TOUCHE LTDA

Ni.*****860,005,813

C E R T I F I C A

Que por Documento Privado del 25 de Junio de 2010, otorgado en Bogota, por DELOITTE & TOUCHE LTDA. inscrito en esta Cámara de Comercio, el 14 de Julio de 2010 bajo el Nro 160,524 del libro respectivo, fueron hechos los siguientes nombramientos:

Cargo/Nombre

Identificación

Designado: Revisor Fiscal Principal

Aguillon Rojas Sandra Milena

CC.*****47,436,442

Designado: Revisor Fiscal Suplente

Prada Sanchez Nubia Marcela

CC.***1,032,358,923

C E R T I F I C A

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,

*** CONTINUA ***

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2010/08/10

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OPERACION: 03R050810087

PAGINA: 6

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

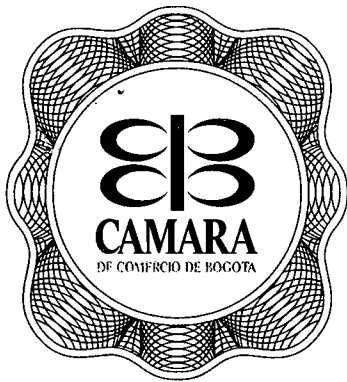
C E R T I F I C A

Que segun Documento Privado de fecha 10 de Octubre del 2.000, inscrito en esta Camara 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 Camara de Comercio de Barranquilla bajo el No.1.872 del libro respectivo, para que en representacion 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.-----

C E R T I F I C A

Que por Escritura Pública No. 2,404 del 28 de Mayo de 2009, otorgada en la Notaria la. de Bogota cuya parte pertinente se inscribió en esta Cámara de Comercio, el 02 de Julio de 2009 bajo el No. 3,948 del libro respectivo,-----
consta que el señor LUIS ALBERTO PALACIOS ARAGON con CE No.319788, en su calidad de Representante Legal de GYNOPHARM S.A., manifesto que confiere poder general, amplio y suficiente a la Doctora -----
CAROLINA MARIA ROMERO CERON, identificada con cedula de ciudadanía numero 52.352.190, para que en nombre de la sociedad GYNOPHARM -----
S.A., promueva y defienda los intereses de la sociedad judicial y extrajudicialmente, en toda especie de gestiones y actuaciones ante las autooridades administrativas o jurisdiccionales en especial ----
para: a) Recibir notificaciones de cualesquiera tipo de actos -----
emanados de las autoridades administrativas o judiciales. b) -----
Presentar recursos por la via administrativa o judicial, renunciar a terminos, desistir, conciliar, transigir y modificar. c) Elevar peticiones y solicitar informacion a las autoridades -----

*** CONTINUA ***



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* 9 5 5 1 4 1 5 1 *

18

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE BARRANQUILLA

FECHA: 2010/08/10

HORA: 10:45:56

OPERACION: 03R050810087

PAGINA: 7

administrativas y jurisdiccionales. d) Presentar demandas ante las autoridades administrativas y judiciales.-----

C E R T I F I C A

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.

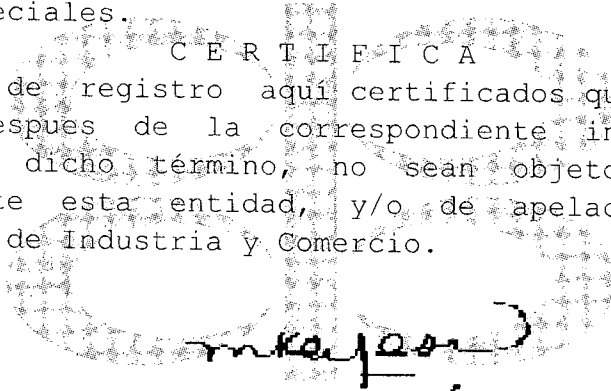
C E R T I F I C A

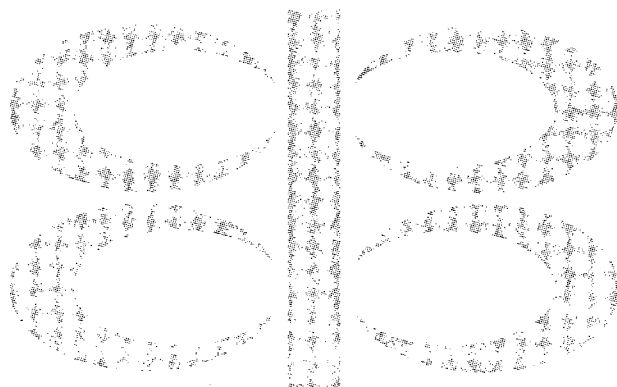
Que su última Renovación fue el: 31 de Marzo de 2010.

La información sobre embargos de establecimiento se suministra en Certificados de Matrícula, la de contratos sujetos a registro, en Certificados Especiales.

C E R T I F I C A

Que los actos de registro aquí certificados quedan en firme cinco días hábiles después de la correspondiente inscripción, siempre que, dentro de dicho término, no sean objeto de los recursos de reposición ante esta entidad, y/o de apelación para ante la Superintendencia de Industria y Comercio.





16

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 09-041709- -00004-0000

Fecha: 2010-08-19 14:59:04 Dep. 2020 DIR.NUEVASCR
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 10 - 68,433
FECHA : AGOSTO 19 DE 2010

**** CONSIGNACION ****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	Nº. PAGO	FECHA PGO	Vr. PAGO
EYNOPHARM S.A.S	CONSIGNACION	BANCO DE BOGOTA	062754387	353965883	13/08/2010	295,000.00
EYNOPHARM S.A.S	CONSIGNACION	BANCO DE BOGOTA	062754387	355160942	13/08/2010	295,000.00
EYNOPHARM S.A.S	CONSIGNACION	BANCO DE BOGOTA	062754387	355160564	13/08/2010	295,000.00

**** CONCEPTO ****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-04	PRESENTACION DE OBSERVACIONES	
12		MARCAS Y LEMAS COMERCIALES	295,000.00
		TOTAL :	\$ 295,000.00

SON: DOSCIENTOS NOVENTA Y CINCO MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

ANEXO 1

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
3 June 2004 (03.06.2004)

PCT

(10) International Publication Number
WO 2004/045615 A1

(51) International Patent Classification⁷: **A61K 31/473**, A61P 1/08 (74) Agent: **LEISSLER-GERSTL**, Gabriele; Eisenführ, Speiser & Partner, Arnulfstr. 25, 80335 München (DE).

(21) International Application Number:
PCT/IB2003/005567

(22) International Filing Date:
6 November 2003 (06.11.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/426,829 15 November 2002 (15.11.2002) US

(71) Applicant (for all designated States except US):
HELSINN HEALTHCARE SA [CH/CH]; P.O. Box 357, CH-6915 Pambio-Noranco, Lugano (CH).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **MACCIOCCHI**, Alberto [CH/CH]; Pizzo Ferraro, CH-6807 Taverne (CH). **CANTOREGGI**, Sergio [CH/CH]; Via Ai Ronchi, 37, CH-6934 Vezia (CH). **BRAGLIA**, Enrico [CH/CH]; Via Pian Scairolo 9, CH-6912 Pazzallo (CH). **BRAGLIA**, Riccardo [CH/CH]; Via Pian Scairolo 9, CH-6912 Pazzallo (CH).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, 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, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/045615 A1

(54) Title: **PALONOSETRON FOR THE TREATMENT OF CHEMOTHERAPY-INDUCED EMESIS**

(57) Abstract: Methods and compositions for reducing chemotherapy and radiotherapy induced emesis with 5-HT₃ receptor antagonists are disclosed, especially with palonosetron.

PALONOSETRON FOR THE TREATMENT OF CHEMOTHERAPY-INDUCED EMESIS

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FIELD OF THE INVENTION

The present invention relates to methods for reducing chemotherapy and radiotherapy induced emesis with 5-HT₃ receptor antagonists. In particular, the invention relates to methods for reducing chemotherapy and radiotherapy induced emesis with palonosetron.

BACKGROUND OF THE INVENTION

Emesis is a devastating consequence of cytotoxic chemotherapy and radiotherapy that drastically affects the quality of life of people undergoing such treatment. In recent years a class of drugs referred to as 5-HT₃ (5-hydroxytryptamine) receptor antagonists has been developed that treat such emesis by antagonizing cerebral functions associated with the 5-HT₃ receptor. See *Drugs Acting on 5-Hydroxytryptamine Receptors*: The Lancet Sep. 23, 1989 and refs. cited therein. Drugs within this class include ondansetron, granisetron and dolasetron, as disclosed in U.S. Pat. Nos. 4,695,578, 4,753,789, 4,929,632, 5,240,954, 5,578,628, 5,578,632, 5,922,749, 5,622,720, 5,955,488, and 6,063,802 (ondansetron), 4,906,755, 5,011,846, and 4,906,755 (dolasetron), and 4,886,808, 4,937,247, 5,034,398 and 6,294,548 (granisetron).

These 5-HT₃ antagonists are typically administered intravenously shortly before chemotherapy or radiotherapy is initiated, and can be administered more than once during a cycle of chemotherapy or radiotherapy. For example, when a chemotherapeutic agent is administered more than once in a cycle (as for example on days 1-7 in a 28 day chemotherapy cycle), the 5-HT₃ antagonist can be administered on each of days 1-7 for optimum anti-emetogenic effect. Because some chemotherapeutic agents can induce emesis over extended periods of several days even when they are administered only once, it would be desirable to administer an emesis-inhibiting drug such as a 5-HT₃ antagonist

every day until the risk of emesis has substantially subsided. The present class of 5-HT₃ antagonists has not proven especially helpful meeting this need, however, because the 5-HT₃ receptor antagonists currently marketed have proven to be less effective in controlling delayed nausea and vomiting than they are at controlling acute emesis. Sabra, K, *Choice of a 5HT₃ Receptor Antagonist for the Hospital Formulary*. EHP, Oct. 1996;2 (suppl 1):S19-24.

Each of the currently available 5-HT₃ antagonists also suffers from one or more of the following deficiencies which limits its therapeutic utility: potency, duration of effect, window of therapeutic efficacy, ease of dosing, side effects, and certainty of the dosing regimen. Sabra, K (1996) (supra). Although side effects are typically mild to moderate and transient, they include headache, lightheadedness or dizziness, abdominal pain or cramping, constipation, sedation and fatigue, elevations in hepatic transaminases and/or bilirubin, and electrocardiographic changes. Gregory, RE and Ettinger, DS, *5HT₃ receptor antagonists for the prevention of chemotherapy-induced nausea and vomiting. A comparison of their pharmacology and clinical efficacy*. Drugs, Feb 1998;55(2):173-189.

Various patents and references disclose classes of compounds useful as emesis-inhibiting agents and 5-HT₃ antagonists. For example, Ponchant et al., "Synthesis of 5-¹²⁵I-Iodo-Zacopride, A New Probe for 5-HT₃ Receptor Sites," J. Lab. Cps. and Radiopharm., Vol. XXIX, No. 10, pp. 1147-1155 (1991) discloses substituted 3-quinuclidinyl benzamides useful for 5-HT₃ serotonin receptor binding. U.S. Pat. No. 4,717,563 to Alphin et al., discloses a method of controlling emesis caused by non-platinum anti-cancer drugs utilizing particular N-3-quinuclidinyl benzamides and thiobenzamides. U.S. Pat. No. 4,820,715 to Monkovic et al. discloses substituted 3-quinuclidinyl benzamide compounds which are asserted to be useful for the treatment of emesis, such as chemotherapy-induced emesis, and/or treatment of disorders related to impaired gastric motility. U.S. Patent No. 5,202,303 to Berger et al. discloses a class of benz[de]isoquinolin-1-ones that act as 5-HT₃ receptor antagonists. Species disclosed in the patent include palonosetron. According to this patent, the class of compounds is useful to treat emesis, gastrointestinal disorders, anxiety, depressive states, and pain. The patent does not disclose any particular data for determining a suitable therapeutic regimen

such as the potency of the compounds, the serum half life of the compounds, dose response data, or duration of effect.

One of the greatest challenges in drug dosing, especially when multiple doses are administered over a period of a few days, is to find a dose that is well-tolerated and consistently efficacious throughout the dosing regimen. Finding an optimum dose is complicated by such factors as serum half-life, dosing/efficacy relationships, and, in the case of anti-emetic drugs, the variability of the chemotherapeutic regimen with which the drugs will be administered and the types of emesis induced (i.e. delayed v. acute emesis and moderately v. highly emetogenic chemotherapy). This challenge is particularly acute when devising single unit dose formulations of the anti-emetic drug that is efficacious over a range of body weights, because single unit dose forms are designed typically to prevent nurses and doctors from titrating the dose in the clinic.

OBJECTS OF THE INVENTION

It is an object of the present invention to provide methods of inhibiting emesis using 5-HT₃ receptor antagonists that have heightened potency, and that can be administered in lower doses to yield fewer incidences of unwanted side effects.

It is another object of the invention to provide methods of inhibiting and relieving acute and delayed emesis induced by chemotherapeutic agents or radiotherapy, and drugs having the capacity to inhibit and relieve such acute and delayed emesis.

Another object of the present invention is to provide a uniform defined dose of palonosetron that can be administered to a patient of nearly any body weight in successive 24 hour periods to control immediate and delayed emesis.

Still another object of the present invention is to provide 5-HT₃ antagonists that possess increased plasma half-life and prolonged *in vivo* activity.

Another object of the invention is to provide greater flexibility when administering emesis-inhibiting agents in advance of chemotherapeutic regimens or radiotherapy, by increasing the size of the window for pretreatment.

Yet another object of the invention is to provide greater flexibility when administering an emesis-inhibiting agent, by reducing the time required to administer a bolus of the emesis-inhibiting agent

Still another object of the present invention is to provide more definite regimens for the treatment of chemotherapeutically or radiotherapeutically induced emesis, by preventing doctors from prescribing unnecessarily increased dosages of palonosetron, and allowing doctors to switch to other anti-emetic agents when palonosetron does not prove effective rather than increasing the dose.

SUMMARY OF INVENTION

Contrary to published reports that 5-HT₃ antagonists have minimal benefit in the treatment or prevention of delayed emesis, the inventors have surprisingly discovered that palonosetron alleviates and prevents acute and delayed emesis in both moderately and highly emetogenic chemotherapy regimens, and that palonosetron is substantially superior to both ondansetron and dolasetron in its ability to prevent and alleviate nausea and vomiting that occurs more than 24 hours after the initiation of moderately emetogenic chemotherapy. Therefore, in one embodiment the invention provides a method of treating acute and delayed emesis in a patient undergoing emetogenic chemotherapy or radiotherapy comprising administering a treatment effective amount of palonosetron. The treatment effective amount is preferably one of the doses disclosed in greater detail elsewhere in this document.

The inventors have also made a series of discoveries that support a surprisingly effective and versatile clinical regimen for the treatment and prevention of emesis using palonosetron. In particular, the inventors have discovered:

- that palonosetron can treat and prevent emesis induced by chemotherapy and radiotherapy at levels of only about 1/10th the levels of other 5-HT₃ antagonists;
- that palonosetron has a plasma half-life of about 40 hours; and
- that the efficacy of palonosetron plateaus over a broad range of doses ranging from about 30 μ g/kg to about 90 μ g/kg.

Based upon the foregoing discoveries, the inventors have determined that 0.25 mg/day of palonosetron is a particularly effective and versatile dose of palonosetron for use in the clinic because the dose is effective when used only once in a chemotherapy or radiotherapy cycle, but it is also effective when administered on successive days because, in spite of the long half-life of palonosetron and a concomitant build-up of palonosetron

during the multiple doses, consistent efficacy can be expected from each dose of palonosetron due to the observed plateau effect. Moreover, such efficacy can be expected over a wide range of patient body weights.

Therefore in another embodiment the invention provides a method of treating chemotherapy or radiotherapy-induced emesis in a patient comprising administering a dose of 0.25 mg of palonosetron to the patient. In another embodiment the invention provides single unit dosage forms of palonosetron that comprise 0.25 mg of palonosetron.

The surprising potency of palonosetron, the extended plasma half-life of palonosetron, and the plateau dosing phenomena observed for palonosetron, also have a number of other practical advantages including:

- The potency of palonosetron allows for greater cost efficiencies because lesser quantities of palonosetron are needed.
- The potency of palonosetron also allows the manufacturer to formulate the drug at reduced concentrations. This advantage is of particular significance in the formulation of palonosetron because palonosetron has been found to be most stable at lower concentrations. This advantage is also significant from a convenience standpoint because the palonosetron can be sufficiently concentrated to be intravenously administered as a bolus in only about from 10 to 30 seconds.
- The extended plasma half-life reduces even further the quantity of palonosetron that must be administered to treat emesis.
- The extended half-life allows the palonosetron to be administered at intervals of about 24 hours, or only once in certain therapeutic settings.
- The extended half-life allows greater flexibility in a clinical setting by allowing the drug to be administered over a larger window of time preceding the administration of chemotherapy or radiotherapy.
- The extended half-life and plateau dosing phenomena combine to provide more certainty to the regimen by assuring the physician that a further dose of palonosetron in a session is not warranted within a particular window of time even if emesis is experienced.

- The extended half-life and plateau dosing phenomena further combine to provide more certainty to the regimen by avoiding the tendency of physicians to increase the dose of palonosetron in subsequent sessions if emesis is experienced in a prior session.

5

DEFINITIONS

“Ampule” means a small sealed container of medication that is used one time only, and includes breakable and non-breakable glass ampules, breakable plastic ampules, miniature screw-top jars, and any other type of container of a size capable of holding only one unit dose of palonosetron (typically about 5 mls.).

10

“Animal” includes humans, non-human mammals (e.g., dogs, cats, rabbits, cattle, horses, sheep, goats, swine, and deer) and non-mammals (e.g., birds and the like). While the methods disclosed herein are generally applicable to people, they are applicable as well to animals.

15

“Chemotherapeutic agents” include a variety of classes of compounds for treating proliferative disorders including alkylating agents, antimetabolites, natural products, enzymes, biological response modifiers, miscellaneous agents, radiopharmaceuticals (for example, Y-90 tagged to hormones or antibodies), hormones and antagonists, such as those listed below.

Antiangiogenesis Agents: Angiostatin, Endostatin.

20

Alkylating Agents: Nitrogen Mustards such as Mechlorethamine, Cyclophosphamide, Ifosfamide, Meiphalan (L-sarcolysin), and Chlorambucil; Ethylenimines and Methylnmelamines such as Hexamethylnmelamine and Thiotepa; Alkyl Sulfonates such as Busulfan; Nitrosoureas such as Carmustine (BCNU), Lomustine (CCNU), Semustine (methyl-CCNU), and Streptozocin (STR); and Triazenes such as

25

Dacarbazine (DTIC; dimethyltriazenoimidazole-carboxamide).

Antimetabolites: Folic Acid Analogs such as Methotrexate (amethopterin);

Pyrimidine Analogs such as Fluorouracil (5-fluorouracil; 5-FU), Floxuridine (fluorodeoxyuridine; FUdR), and Cytarabine (cytosine arabinoside); Purine Analogs and Related Inhibitors such as Mercaptopurine (6-mercaptopurine; 6-MP), Thioguanine (6-thioguanine: TG), and Pentostatin (2'-deoxycyfoformycin); Vinca Alkaloids such as

30

25
Vinblastine (VLB), and Vincristine; and Epipodophylotoxins such as Etoposide and Teniposide.

Natural Products: Antibiotics such as Dactinomycin (actinomycin D), Daunorubicin (daunomycin; rubidomycin), Doxorubicin, Bleomycin, Plicamycin
5 (mithramycin), and Mitomycin (mitomycin C); Enzymes such as L-Asparaginase; and Biological Response Modifiers such as Interferon-alfa.

Miscellaneous Agents: Platinum Coordination Complexes such as Cisplatin (cis-DDP) and Carboplatin; Mixtozantrone; Hydroxyurea; Procarbazine (N-methylhydrazine, MIH); Mitotane (o,p'-DDD); Aminoglutethimide; Adrenocorticosteroids such as
10 Prednisone; and Progestins such as Hydroxprogesterone caproate, Medroxyprogesterone acetate, and Megestrol acetate.

Hormones and Antagonists: Estrogens such as Diethylstilbestrol and Ethinyl estradiol; Antiestrogens such as Tamoxifen; Androgens such as Testosterone propionate Fluxomyesterone; Antiandrogens such as Flutamide (prostate); and Gonadotropin-
15 Releasing Hormone Analog such as Leuprolide.

Throughout this specification the word "comprise," or variations such as "comprises" or "comprising," will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of
any other element, integer or step, or group of elements, integers or steps

20 "Disease" specifically includes any unhealthy condition of an animal or part thereof and includes an unhealthy condition which may be caused by, or incident to, medical or veterinary therapy applied to that animal, i.e., the side effects of such therapy. Thus, disease here includes the emesis caused by therapy with agents having emetogenic side effects, in particular by therapy for cancer, such as chemotherapy with
25 chemotherapeutic agents and radiotherapy.

"Emesis", for the purposes of this application, will have a meaning that is broader than the normal, dictionary definition and includes not only vomiting, but also nausea and retching.

"Delayed emesis" means emesis that occurs greater than about 24 hours after
30 initiation of an emesis inducing chemotherapeutic or radiotherapeutic event. Delayed

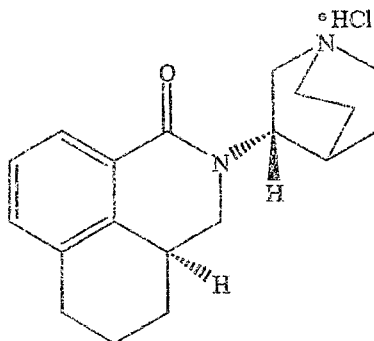
emesis thus includes emesis that occurs up to 2, 3, 4, or even 5 days after a chemotherapeutic or radiotherapeutic event.

"Acute emesis" refers to emesis that involves vomiting within 24 hours of initiation of an emesis inducing chemotherapeutic or radiotherapeutic event.

5 "Moderately emetogenic chemotherapy" refers to chemotherapy in which the emetogenic potential is comparable or equivalent to the emetogenic potential of carboplatin, cisplatin $\leq 50 \text{ mg/m}^2$, cyclophosphamide $< 1500 \text{ mg/m}^2$, doxorubicin $> 25 \text{ mg/ms}$, epirubicin, irinotecan, or methotrexate $> 250 \text{ mg/m}^2$.

"Highly emetogenic chemotherapy" refers to chemotherapy in which the
10 emetogenic potential is comparable or equivalent to the emetogenic potential of cisplatin $\geq 60 \text{ mg/m}^2$, cyclophosphamide $> 1500 \text{ mg/m}^2$, or dacarbazine.

"Palonosetron" means (3aS)-2,3,3a,4,5,6-Hexahydro-2-[(S)-1-Azabicyclo[2.2.2]oct-3-yl]2,3,3a,4,5,6-hexahydro-1-oxo-1H-benz[de]isoquinoline hydrochloride, and is preferably present as the monohydrochloride. Palonosetron
15 monohydrochloride can be represented by the following chemical structure:



20 "Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary use as well as human pharmaceutical use.

"Pharmaceutically acceptable salts" means salts which are pharmaceutically
25 acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with inorganic acids such as hydrochloric

acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or with organic acids such as acetic acid, propionic acid, hexanoic acid, heptanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, o-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedithiosulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid p-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, p-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid, 4,4'-methylenebis(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid, and the like.

In addition, pharmaceutically acceptable salts may be formed when an acidic proton present is capable of reacting with inorganic or organic bases. Acceptable inorganic bases include sodium hydroxide, sodium carbonate, potassium hydroxide, aluminum hydroxide and calcium hydroxide. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine and the like.

"Therapeutically effective amount" means that amount which, when administered to an animal for treating a disease, is sufficient to effect such treatment for the disease.

"Treating" or "treatment" of a disease includes: (1) preventing the disease from occurring in an animal which may be predisposed to the disease but does not yet experience or display symptoms of the disease, (2) treating the disease, i.e., arresting its development, or (3) relieving the disease, i.e., causing regression of the disease.

DETAILED DISCUSSION

One embodiment of the present invention is premised upon the discovery that palonosetron is surprisingly superior to other 5-HT₃ antagonists in its ability to treat delayed emesis, while exhibiting remarkable efficiency at treating acute emesis as well. Thus, in one embodiment, the invention provides a method of treating chemotherapy or radiotherapy induced delayed and acute emesis comprising administering a treatment-

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effective amount of palonosetron. The method is effective for the treatment of emesis induced by both moderately emetogenic chemotherapy and highly emetogenic chemotherapy.

In another embodiment the invention provides a method for treating acute and/or delayed emesis comprising (a) administering to a human or other animal from about 1 to about 10 $\mu\text{g/kg}$ of palonosetron, and (b) administering to said human or other animal an emesis inducing amount of a chemotherapeutic agent or radiotherapy. While larger doses of palonosetron of up to about 30, 60, or 90 $\mu\text{g/kg}$, can be administered effectively to reduce emesis, it has surprisingly been found that the effectiveness of palonosetron typically plateaus at these lower concentrations in the chemotherapeutic regimens tested. Therefore, in a preferred embodiment, from about 3 to about 10 $\mu\text{g/kg}$ of palonosetron is administered. In another embodiment the palonosetron is administered in the absence of a steroid such as dexamethasone.

In another embodiment the invention provides a method of treating chemotherapy or radiotherapy-induced emesis in a patient comprising administering a dose of 0.25 mg of palonosetron to the patient. This dose has been found to be effective over a range of body weights from about 40 to about 120 kilograms, and can conveniently be provided in single unit dose ampules that need not be titrated based upon a patient's body weight within this range. The dose is effective to treat chemotherapy-induced delayed and acute emesis. In addition, the dose is effective for the treatment of emesis induced by both moderately emetogenic chemotherapy and highly emetogenic chemotherapy.

A particularly surprising advantage of the lower dosages required of palonosetron derives from the fact that the stability of palonosetron increases in solution as its concentration decreases. The potency of palonosetron thus allows the palonosetron to be formulated in stable compositions comprising a wide range of palonosetron concentrations, preferably from about 0.01 mg/ml to about 0.20 mg/ml palonosetron, most preferably at a concentration of about 0.05 mg/ml. Thus, in one particular embodiment the palonosetron is supplied in ampules that comprise 5 ml. of solution, which equates to about 0.25 mg of palonosetron at a concentration of about 0.05 mg/ml.

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The enhanced stability allows the palonosetron to be stored for extended periods of time, exceeding about 1 month, 3 months, 6 months, 1 year, or 18 months, but preferably not extending beyond 30 months (we are testing the stability, which shall be included in the FDA file). This enhanced stability is seen in a variety of storage conditions, including room temperature.

The method can be practiced using virtually any method of administration including oral, systemic (e.g., transdermal, intranasal or by suppository) or parenteral (e.g., intramuscular, intravenous or subcutaneous). In a preferred embodiment the palonosetron is administered as an oral liquid or intravenously, and most preferably the palonosetron is administered intravenously.

Another particular advantage associated with the lower dosages of palonosetron is the ability to administer the drug in a single intravenous bolus over a short, discrete time period. This time period generally extends from about 10 to about 60 seconds, or about 10 to about 40 seconds, and most preferably is about 10 to 30 seconds.

Still other embodiments pertain to the sequence and timing of steps in which the method is performed. Although the method can be performed in any sequence, in a preferred embodiment step (a) (the palonosetron administration) precedes step (b) (the chemotherapy or radiotherapy administration) in sequence. Moreover, while step (a) can be performed over a large window of time preceding step (b), from immediately before step (b) to as long as 1, 2, 5, 8, or 10 hours before step (b), the palonosetron is preferably administered from about 15 minutes to about 2 hours before the chemotherapeutic agent or radiotherapy, more preferably from about 15 minutes to about 1 hour before the chemotherapeutic agent or radiotherapy, and most preferably about 30 minutes before the chemotherapy agent or radiotherapy.

The methods of the present invention are preferably performed in the context of chemotherapeutic or radiotherapy cycles, in which an intensive regimen of chemotherapy or radiotherapy is administered over a defined time period, followed by an extended recovery period, and a subsequent cycle in which the therapy and recovery sequence is repeated. An intensive regimen of chemotherapy may comprise only one administration of a chemotherapeutic agent, or it may comprise several days of administering the same

chemotherapeutic agent. Similarly, the regimen may include the administration of more than one chemotherapeutic agents. Moreover, one or more of the chemotherapeutic agents may induce acute and/or delayed emesis.

Palonosetron is preferably administered in conjunction with the chemotherapy or radiotherapy based upon when emesis is most likely to be experienced, at time intervals of about 24 hours. For example, if an emesis inducing chemotherapeutic agent that induces acute emesis and not delayed emesis is administered only once during a cycle of chemotherapy (i.e. in one session), palonosetron will be administered only once as well. If the chemotherapeutic agent induces acute and delayed emesis, then palonosetron will preferably be administered at the initiation of the chemotherapy and every 24 hours thereafter until the emesis has subsided. Similarly, if an emesis inducing agent is administered more than once during a chemotherapy cycle (i.e. in more than one session), then palonosetron will preferably also be administered more than once every 24 hours.

The methods of the present invention are useful for treating emesis induced by a wide range of chemotherapeutic agents and radiotherapies discussed above, but are particularly useful when employed in conjunction with cisplatin, cyclophosphamide, carmustine, dicarbazine, actinomycin D, mechlorethamine, carboplatin, doxorubicin, epirubicin, irinotecan, methotrexate, and dacarbazine. The methods have also been found to be particularly useful when used in conjunction with highly emetogenic chemotherapy, especially when using chemotherapeutic agents that are typically associated with extended periods of emesis, or delayed onset of emesis. In various embodiments, the chemotherapeutic agent induces emesis for a period of at least about 24 hours, 48 hours, 72 hours, or 5 days. For example, in one embodiment the chemotherapeutic agent is cisplatin or cyclophosphamide, and in still further preferred embodiments the cisplatin is administered at a dose exceeding about 30, 40, 50, 60, or 70 mg/m², and the cyclophosphamide is administered at a dose exceeding about 500, 600, 700, 800, 900, 1000, or 1100 mg/m².

The plateau effects observed with increasing doses of palonosetron, combined with its extended half-life, further combine to inform the prescribing physician of appropriate regimens to be followed when a patient is at least partially non-responsive to palonosetron. For example, under some circumstances the physician will be assured that

he should switch the patient from palonosetron in a subsequent session rather than administer a higher dose of palonosetron. Therefore, in another embodiment the invention provides a method of preventing chemotherapy induced emesis comprising: (1) in a first chemotherapeutic session: administering to a human or other animal a first
5 amount of palonosetron; and administering to said human or other animal an emesis inducing amount of a chemotherapeutic agent; (2) assessing the effectiveness of the palonosetron; and (3) in a subsequent chemotherapeutic session, if said human or other animal is at least partly non-responsive to said palonosetron in said first chemotherapeutic session, administering to said human or other animal a therapeutically
10 effective amount of a second anti-emetic compound; wherein the subsequent chemotherapeutic session is performed without an intervening chemotherapeutic session in which a second amount of palonosetron higher than the first amount is administered.

The plateau dosing effect, when combined with the extended serum half life, can also render the dosing regimen in some circumstances more certain by avoiding the
15 tendency of physicians to prematurely administer additional doses of palonosetron in a single therapeutic session if emesis is experienced. Thus, in another embodiment the invention provides a method of preventing chemotherapy induced emesis comprising, (1) in one chemotherapeutic session: administering to a human or other animal a first dose of palonosetron; and administering to said human or other animal an emesis inducing
20 amount of a chemotherapeutic agent; (2) assessing the effectiveness of the palonosetron; and (3) if said human or other animal is at least partly non-responsive to said first dose of palonosetron, not administering a second dose of palonosetron for at least about 20, 24, 28, or 32 hours after step (a) or (b).

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PHARMACEUTICAL COMPOSITIONS

Although the foregoing discussion has focused upon intravenous administration of palonosetron because that is the preferred mode of administration, the methods of the present invention can be performed by administering palonosetron by any one of the following routes: oral, systemic (e.g., transdermal, intranasal or by suppository) or
30 parenteral (e.g., intramuscular, intravenous or subcutaneous).

Oral compositions will generally include an inert diluent or an edible carrier. They may be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition.

The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring. When the dosage unit form is a capsule, it can contain, in addition to material of the above type, a liquid carrier such as a fatty oil. In addition, dosage unit forms can contain various other materials which modify the physical form of the dosage unit, for example, coatings of sugar, shellac, or other enteric agents.

The compound can be administered as a component of an elixir, suspension, syrup, wafer, chewing gum or the like. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors.

The compound or a pharmaceutically acceptable prodrug or salts thereof can also be mixed with other active materials that do not impair the desired action, or with materials that supplement the desired action, such as antibiotics, antifungals, anti-inflammatories, or other antivirals, including other nucleoside compounds. Solutions or suspensions used for parenteral, intradermal, subcutaneous, or topical application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parental

preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

If administered intravenously, preferred carriers are physiological saline or phosphate buffered saline (PBS).

- 5 Preferably the pharmaceutical composition is administered in a single unit dosage form for continuous treatment or in a single unit dosage form ad libitum when relief of symptoms is specifically required.

EXAMPLES

10 Example 1: Antiemetic Effects of Palonosetron in Animal Models

The antiemetic effects of intravenously and orally administered palonosetron were assessed in male and female dogs (sexes combined). Antineoplastic agents employed in these experiments included cisplatin (3 mg/kg), dacarbazine (30 mg/kg), mechlorethamine (0.4 mg/kg) and actinomycin D (0.15 mg/kg).

- 15 Palonosetron and comparator drugs were administered prior to or after antineoplastic agents and animals were observed for the number of emetic episodes. Mean numbers of episodes were computed and the statistical significance of differences between treatment groups were determined with Dunnett's t test. Solutions of palonosetron and comparator drugs (ondansetron and granisetron) were prepared in
20 distilled water. Vehicle control groups received distilled water.

- The therapeutic effects of intravenously and orally administered palonosetron were compared to those of ondansetron and vehicle in cisplatin-treated dogs. When administered by the intravenous route, both palonosetron (0.1 mg/kg) and ondansetron (1.0 mg/kg) reduced the number of emetic episodes during the five-hour period following
25 administration of cisplatin 3.0 mg/kg. Palonosetron was statistically significantly more potent than ondansetron based on the mean number of emetic episodes observed (2.20 and 6.83 for palonosetron and ondansetron, respectively, compared with 12.50 for vehicle control).

- 30 In a different study, palonosetron and ondansetron were assessed for their relative abilities to reverse cisplatin-induced emesis. In these experiments dogs received

intravenous injections of palonosetron, ondansetron, or vehicle one hour after the intravenous administration of 3.0 mg/kg cisplatin. Each animal was observed continuously for five hours following cisplatin administration for the number of emetic episodes. The results of this experiment are summarized in Table 1.

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Table 1. Therapeutic Effect of Intravenously Administered Palonosetron and Ondansetron on Cisplatin-Induced Emesis in Dogs

Treatment	N	Intravenous Dose ($\mu\text{g/kg}$)	Emetic Episodes (mean $\pm$ SD)
Vehicle control	6	0.0	13.50 $\pm$ 5.89
Palonosetron	6	0.3	13.16 $\pm$ 6.11
	6	1.0	7.16 $\pm$ 4.26 ^a
	6	3.0	4.33 $\pm$ 4.03 ^b
	6	10.0	4.50 $\pm$ 5.24 ^b
	6	30.0	1.33 $\pm$ 1.21 ^b
	6	100.0	1.67 $\pm$ 1.83 ^b
	6	300.0	3.33 $\pm$ 3.01 ^b
Ondansetron	6	1.0	16.16 $\pm$ 5.14
	6	3.0	13.33 $\pm$ 4.17
	6	10.0	13.33 $\pm$ 3.01
	6	30.0	8.33 $\pm$ 3.20
	6	100.0	4.83 $\pm$ 2.40 ^b
	6	300.0	1.00 $\pm$ 2.00 ^b
	6	1000.0	1.16 $\pm$ 0.40 ^b

^a Significantly less than vehicle control, $p < 0.05$.

10 ^b Significantly less than vehicle control, $p < 0.01$.

The statistically minimally effective dose level was 1.0 $\mu\text{g/kg}$ for palonosetron and 100 $\mu\text{g/kg}$ for ondansetron, suggesting that palonosetron was substantially more potent than ondansetron in this experiment.

15 The observation of potency differential was further seen during an experiment in which oral dose-response relationships of palonosetron and ondansetron were compared in cisplatin-treated dogs. Palonosetron, ondansetron or vehicle control were administered by the oral route one hour prior to the administration of cisplatin. Each animal was

observed continuously for five hours following cisplatin administration for the number of emetic episodes. The results of this experiment are summarized in Table 2.

5 **Table 2. Anti-Emetic Effect in Male and Female Dogs of Palonosetron or Ondansetron Orally Administered One Hour Before Cisplatin**

Treatment	N	Oral Dose ($\mu\text{g/kg}$)	Emetic Episodes (mean $\pm$ SD)
Vehicle control	6	0.0	14.16 $\pm$ 7.98
Palonosetron	6	0.3	12.16 $\pm$ 1.94
	6	1.0	12.83 $\pm$ 4.70
	6	3.0	16.16 $\pm$ 5.11
	6	10.0	4.00 $\pm$ 3.79 ^a
	6	30.0	2.66 $\pm$ 1.75 ^a
	6	100.0	0.00 $\pm$ 0.00 ^a
	6	300.0	1.67 $\pm$ 2.04 ^a
Ondansetron	6	1.0	15.50 $\pm$ 3.93
	6	3.0	14.83 $\pm$ 6.49
	6	10.0	12.66 $\pm$ 3.01
	6	30.0	18.33 $\pm$ 8.43
	6	100.0	10.50 $\pm$ 3.14
	6	300.0	3.16 $\pm$ 1.32 ^a
	6	1000.0	2.00 $\pm$ 2.09 ^a

a Significantly less than vehicle control, $p < 0.01$.

10 Pretreatment with both palonosetron and ondansetron reduced the incidences of emetic episodes. Palonosetron exhibited the greater potency as evidenced by a significant reduction in episodes after 10 $\mu\text{g/kg}$ as compared to the minimally effective dose of 300 $\mu\text{g/kg}$ for ondansetron.

Example 2: Duration of Action in Cisplatin-Treated Dogs

15 The durations of action of intravenously administered palonosetron, ondansetron and granisetron in dogs were compared in an experiment, the results of which are shown in Table 3. In this study groups of six dogs received intravenous doses of palonosetron, ondansetron, or granisetron (0.1, 0.15, or 0.04 mg/kg, respectively), or vehicle control 12, 10, 8, 6, 4, 2, or 1 hour prior to the intravenous injection of 3.0 mg/kg of cisplatin.

Table 3. Duration of Action of Intravenously Administered Palonosetron, Ondansetron, or Granisetron in Cisplatin-Dosed Dogs

Pre-Cisplatin (hr)	Treatment	Dose (mg/kg)	Emetic Episodes (mean $\pm$ SD)
12	Vehicle	0	17.33 $\pm$ 4.68
	Palonosetron	0.1	13.17 $\pm$ 6.27
	Ondansetron	0.15	22.00 $\pm$ 8.32
	Granisetron	0.04	15.67 $\pm$ 6.28
10	Vehicle	0	19.33 $\pm$ 5.68
	Palonosetron	0.1	9.83 $\pm$ 4.79 ^b
	Ondansetron	0.15	13.83 $\pm$ 4.58
	Granisetron	0.04	23.00 $\pm$ 5.87
8	Vehicle	0	20.00 $\pm$ 4.94
	Palonosetron	0.1	9.50 $\pm$ 5.50 ^b
	Ondansetron	0.15	15.50 $\pm$ 7.29
	Granisetron	0.04	14.67 $\pm$ 8.69
6	Vehicle	0	17.33 $\pm$ 7.66
	Palonosetron	0.1	5.83 $\pm$ 4.40 ^b
	Ondansetron	0.15	14.17 $\pm$ 6.79
	Granisetron	0.04	21.33 $\pm$ 9.54
4	Vehicle	0	12.67 $\pm$ 2.34
	Palonosetron	0.1	0.33 $\pm$ 0.52 ^b
	Ondansetron	0.15	12.67 $\pm$ 2.07
	Granisetron	0.04	13.83 $\pm$ 7.25
2	Vehicle	0	12.00 $\pm$ 6.20
	Palonosetron	0.1	2.50 $\pm$ 2.43 ^b
	Ondansetron	0.15	10.67 $\pm$ 5.28
	Granisetron	0.04	9.67 $\pm$ 4.46
1	Vehicle	0	13.83 $\pm$ 4.36
	Palonosetron	0.1	1.33 $\pm$ 1.03 ^b
	Ondansetron	0.15	7.83 $\pm$ 4.12 ^b
	Granisetron	0.04	12.33 $\pm$ 4.32

a For each treatment group, $n = 6$ and the vehicle control was distilled water.

b Significantly less than vehicle control, $p < 0.05$ using Fisher's LSD strategy.

Palonosetron exhibited some antiemetic activity when administered as long as 10 hours before the injection of cisplatin. Ondansetron reduced emetic episodes only after a one-hour pretreatment period. Granisetron was without antiemetic effect in these experiments. Palonosetron did not protect when administered 12 hours before cisplatin. In an earlier experiment, a higher dose of ondansetron (0.3 mg/kg, IV) exhibited protective effects when administered as long as seven hours prior to injection of cisplatin. In that experiment, a dose of 0.03 mg/kg of palonosetron was similarly effective. The results of these experiments support the conclusion that the duration of antiemetic action of palonosetron is longer than that of ondansetron, and that a higher dose of ondansetron is required to achieve an equivalent effect.

Example 3: Relationship Between Systemic Exposure and Antiemetic Effect

An experiment was conducted to study the relationship between plasma concentration of palonosetron and protection of dogs against cisplatin-induced emesis. Groups of dogs received oral doses of palonosetron (0, 100, 316, or 1000 $\mu\text{g/kg}$) or vehicle control 30 minutes prior to the injection of cisplatin. Plasma concentrations of palonosetron were determined by an HPLC-radioimmunoassay method at 0, 0.25, 0.5, 1, 2, 4, 8, 24, and 48 hours after administration of palonosetron and systemic exposure was expressed as AUC_{0-4 hr}. Results are summarized in Table 4.

Table 4. Systemic Exposure of Palonosetron (AUC_{0-4hr}) in Dogs After Intravenous Administration and Effects on Cisplatin-Induced Emesis

Palonosetron ($\mu\text{g/kg}$)	N	AUC _{0-4hr} (mean $\pm$ SD)	Emetic Episodes (mean $\pm$ SD)
0 (vehicle)	6	0.00 $\pm$ 0.00 ^a	15.83 $\pm$ 3.43
100	6	10.59 $\pm$ 7.24 ^a	1.83 $\pm$ 1.60 ^b
316	6	30.64 $\pm$ 12.02 ^a	4.50 $\pm$ 6.83 ^b
1000	6	76.07 $\pm$ 50.39 ^a	5.67 $\pm$ 5.32 ^b

^a Significantly different from all other AUCs, $p < 0.01$.

^b Significantly different from controls, $p < 0.05$.

Systemic exposure to palonosetron, as estimated by computed AUC_{0-4hr} values, were approximately dose-proportional over the range studied, however, a relationship between systemic exposure and magnitude of antiemetic effect could not be demonstrated. Dogs dosed with palonosetron had significantly fewer emetic episodes than vehicle control animals but there was no evidence of a significant dose-response relationship. The lowest dose tested appeared to be at the response plateau.

Example 4: Antagonism of Emetic Effects of Dacarbazine, Actinomycin D, and Mechlorethamine

The protective effects of palonosetron and ondansetron against emesis caused by the administration of dacarbazine, actinomycin D, or mechlorethamine were assessed in dogs. In these experiments palonosetron, ondansetron or vehicle were administered 2 hours prior to the injection of the antineoplastic agent and animals were observed for 5 hours. The results of these experiments are summarized in Table 5.

Table 5. Effects of Palonosetron and Ondansetron on Dacarbazine-, Actinomycin D-, and Mechlorethamine-Induced Emesis in Dogs

Treatment ^a	Dose (mg/kg)	Emetic Episodes (mean $\pm$ SD)		
		Dacarbazine (30.0 mg/kg IV)	Actinomycin D (0.15 mg/kg IV)	Mechlorethamine (0.4 mg/kg IV)
Intravenous Antiemetic				
Vehicle control ^b	0	10.33 $\pm$ 2.66	17.50 $\pm$ 11.43	10.00 $\pm$ 4.69
Palonosetron	0.001	10.17 $\pm$ 2.04	10.00 $\pm$ 0.54 ^c	7.67 $\pm$ 5.05
	0.003	6.67 $\pm$ 4.13	10.83 $\pm$ 2.04	6.00 $\pm$ 4.29
	0.01	1.67 $\pm$ 1.37 ^d	7.17 $\pm$ 3.06 ^d	3.00 $\pm$ 3.52 ^d
	0.03	0.83 $\pm$ 1.17 ^d	5.17 $\pm$ 4.45 ^d	0.17 $\pm$ 0.41 ^d
Ondansetron	0.01	11.50 $\pm$ 5.51	7.67 $\pm$ 2.25 ^d	5.83 $\pm$ 4.31
	0.03	8.17 $\pm$ 2.79	14.67 $\pm$ 4.68	3.50 $\pm$ 2.07 ^c
	0.1	4.83 $\pm$ 2.48 ^d	12.67 $\pm$ 3.45	5.33 $\pm$ 4.68
	0.3	1.33 $\pm$ 0.82 ^d	5.83 $\pm$ 4.45 ^d	4.67 $\pm$ 1.63 ^c
Oral Antiemetic				
Vehicle control	0	14.17 $\pm$ 3.82	14.50 $\pm$ 5.54	9.50 $\pm$ 7.15
Palonosetron	0.003	12.83 $\pm$ 6.68	5.83 $\pm$ 1.47 ^d	4.50 $\pm$ 3.51 ^c
	0.01	6.83 $\pm$ 4.92 ^d	6.67 $\pm$ 3.83 ^d	2.83 $\pm$ 1.94 ^d
	0.03	0.33 $\pm$ 0.52 ^d	3.33 $\pm$ 4.55 ^d	0.33 $\pm$ 0.82 ^d
	0.1	0.00 $\pm$ 0.00 ^d	1.00 $\pm$ 1.67 ^d	0.00 $\pm$ 0.00 ^d

Ondansetron	0.03	10.83 ± 2.72	9.83 ± 7.52	5.67 ± 2.50
	0.1	6.17 ± 5.35 ^d	10.33 ± 4.84	8.50 ± 3.15
	0.3	3.00 ± 3.03 ^d	4.20 ± 1.92 ^d	2.83 ± 3.71 ^d
	1	0.17 ± 0.41 ^d	1.50 ± 1.38 ^d	0.00 ± 0.00 ^d

^a N = Six per treatment group, except in the group receiving 0.3 mg/kg ondansetron po and actinomycin D, in which one dog was dropped due to a dosing error.

^b Vehicle control was distilled water in each instance.

^c Significantly less than vehicle control, $p < 0.05$.

5 ^d Significantly less than vehicle control, $p < 0.01$

Under the conditions of these experiments, both palonosetron and ondansetron, whether administered by the intravenous or oral route, reduced the emetic responses to all three antineoplastic agents. The antiemetic effects of both drugs were generally dose-related and palonosetron was consistently at least 10 times more potent than ondansetron.

Example 5: Human trials assessing the effectiveness of single intravenous doses of palonosetron for the prevention of highly emetogenic chemotherapy-induced nausea and vomiting.

15 A randomized, double-blind, multicenter, dose-ranging Phase II trial was performed to identify the dose response relationship among single I.V. doses of palonosetron. Patients receiving highly emetogenic chemotherapy including cyclophosphamide (>1100mg/m²) and cisplatin (>70mg/m²), commonly associated with delayed emesis, were assigned to one of five dose groups of a single I.V. administration of palonosetron. Palonosetron was administered alone (without dexamethasone) as a 30 second intravenous injection, 30 minutes prior to chemotherapy administration. The primary endpoint was 24-hour complete responses (no emesis, no rescue) (CR). Secondary endpoints included complete control (no emesis, no rescue, mild nausea) (CC) and 5-day CR.

25 161 patients (32 women, 129 men) participated. Key efficacy parameters and results are summarized in Table 6 below. A majority (83.9%) of adverse events were either mild or moderate and not attributed to study medication (86.0%). The most commonly reported adverse events related to study medication include: headache (19.3%); constipation (8.7%), dizziness (2.5%) and abdominal pain (2.5%). No serious drug-related events were reported.

The results demonstrate that in these patients, palonosetron was safe and effective in treating acute emesis and maintained activity through day 5.

Table 6

5

Responders by Dose

Parameters	Palonosetron Dose (mcg/kg)				
	0.3 - 1 (n=29)	3 (n=24)	10 (n=25)	30 (n=24)	90 (n=46)
%CR(24hr)	24	46	40	50*	46
%CC(24hr)	24	39	40	48	46
%CR(Day5)	17	17	32	33	20

*Statistically significant differences ($p < 0.05$) vs. lowest dose group

15 Example 6: Intravenous formulation

Table 7 below presents a representative formulation of palonosetron formulated for intravenous administration.

Table 7

20

Ingredient	Mg
Palonosetron HCl	10-100 mg.
Dextrose Monohydrate Isotonic	q.s. to make
Citric Acid Monohydrate	1.05 mg.
Sodium Hydroxide	0.18 mg.
WFJ	To 1.0 ml.

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Throughout this application, various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this invention pertains.

It will be apparent to those skilled in the art that various modifications and variations can be made in the present invention without departing from the scope or spirit of the invention. Other embodiments of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed

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herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

CLAIMS

What is claimed is:

- 1) A method of treating chemotherapy or radiotherapy-induced acute and delayed emesis comprising administering to an animal a treatment-effective amount of palonosetron.
- 2) The method of claim 1 wherein the chemotherapy or radiotherapy is defined by successive daily administrations of a chemotherapeutic agent or radiotherapy, wherein the method comprises administering palonosetron for two or more successive days.
- 3) The method of claim 1 wherein the chemotherapy is defined by the administration of a single dose of a delayed emesis inducing chemotherapeutic agent during a cycle of chemotherapy, wherein the method comprises administering palonosetron for two or more successive days.
- 4) The method of claim 1 wherein about 0.25 mg of palonosetron is administered.
- 5) The method of claim 1 wherein said palonosetron is administered intravenously.
- 6) The method of claim 1 wherein said palonosetron is administered orally.
- 7) The method of claim 1 comprising, in any order:
 - a) administering to the animal from about 3 to about 10 μ g/kg of palonosetron; and
 - b) administering to the animal an emesis inducing amount of a chemotherapeutic agent.
- 8) The method of claim 7 wherein steps (a) and (b) are performed in sequence.
- 9) The method of claim 7 wherein step (a) is performed about 30 minutes prior to step (b).
- 10) The method of claim 1 wherein said palonosetron is administered as an intravenous bolus over a time period of about 10-30 seconds.
- 11) The method of claim 1 wherein about 0.25 mg of palonosetron is administered in a sterile intravenous solution comprising palonosetron at a concentration of about 0.05 mg/ml.
- 12) The method of claim 1 wherein about 0.25 mg of palonosetron is administered in a sterile intravenous solution comprising palonosetron at a concentration of about

0.05 mg/ml, wherein said palonosetron comprises an age of from about one month to about two years.

- 5
- 13) The method of claim 1 wherein said palonosetron is administered from a single unit dose ampule comprising about 0.25 mg of palonosetron in a sterile injectable solution.
- 14) The method of claim 1 wherein said animal is a human.
- 15) A method of treating chemotherapy or radiotherapy-induced emesis in an animal comprising administering a dose of 0.25 mg of palonosetron to the animal.
- 10
- 16) The method of claim 15 wherein the chemotherapy is defined by successive daily administrations of a chemotherapeutic agent, wherein the method comprises administering 0.25 mg. of palonosetron for two or more successive days.
- 17) The method of claim 15 wherein the chemotherapy is defined by the administration of a single dose of a chemotherapeutic agent and acute and delayed emesis during a cycle of chemotherapy, wherein the method comprises
- 15
- administering 0.25 mg. of palonosetron for two or more successive days.
- 18) The method of claim 15 wherein said palonosetron is administered intravenously.
- 19) The method of claim 15 wherein said palonosetron is administered orally.
- 20) The method of claim 15 wherein said palonosetron is administered as an intravenous bolus over a time period of about 10-30 seconds.
- 20
- 21) The method of claim 15 wherein said palonosetron is administered in a sterile intravenous solution comprising palonosetron at a concentration of about 0.05 mg/ml.
- 22) The method of claim 15 wherein said palonosetron is administered in a sterile intravenous solution comprising palonosetron at a concentration of about 0.05
- 25
- mg/ml, wherein said palonosetron comprises an age of from about one month to about two years.
- 23) The method of claim 15 wherein said emesis is delayed emesis.
- 24) The method of claim 15 wherein said palonosetron is administered from a single unit dose ampule comprising about 0.25 mg of palonosetron in a sterile injectable
- 30
- solution.
- 25) The method of claim 15 wherein said animal is a human.

- 26) A method of preventing chemotherapy or radiotherapy induced emesis comprising:
- a) in a first chemotherapeutic or radiotherapy session:
 - i) administering to a human a first amount of palonosetron; and
 - 5 ii) administering to said human an emesis inducing amount of a chemotherapeutic agent or radiotherapy;
 - b) assessing the effectiveness of the palonosetron; and
 - c) in a subsequent chemotherapeutic or radiotherapy session, if said human is at least partly non-responsive to said palonosetron in said first
 - 10 chemotherapeutic session, administering to said animal a therapeutically effective amount of a second anti-emetic compound; and
 - d) wherein the subsequent chemotherapeutic session is performed without an intervening chemotherapeutic session in which a second amount of palonosetron higher than the first amount is administered.
- 15 27) A method of preventing chemotherapy or radiotherapy induced emesis comprising, in one chemotherapeutic or radiotherapy session:
- a) administering to a human a first dose of palonosetron; and
 - b) administering to said animal an emesis inducing amount of a chemotherapeutic agent or radiotherapy;
 - 20 c) assessing the effectiveness of the palonosetron; and
 - d) if said human is at least partly non-responsive to said first dose of palonosetron, not administering a second dose of palonosetron for at least 24 hours after step (b).
- 28) A single unit dose of palonosetron comprising an ampule of 0.25 mg of
- 25 palonosetron in a sterile injectable solution.
- 29) The single unit dose of palonosetron of claim 28 wherein said palonosetron is present at a concentration of about 0.05 mg/ml.
- 30) The single unit dose of palonosetron of claim 28 wherein said sterile injectable solution has a pH of about 5.
- 30 31) The single unit dose of palonosetron of claim 28 wherein said palonosetron has an age of from about 1 month to about 2 years.

ANEXO 2



US 20040052824A1

(19) **United States**(12) **Patent Application Publication** (10) **Pub. No.: US 2004/0052824 A1**
Abou Chacra-Vernet et al. (43) **Pub. Date: Mar. 18, 2004**(54) **MICELLAR COLLOIDAL
PHARMACEUTICAL COMPOSITION
CONTAINING A LIPOPHILIC ACTIVE
PRINCIPLE**(30) **Foreign Application Priority Data**

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Chicago, IL 60606 (US)(57) **ABSTRACT**(21) **Appl. No.: 10/465,923**(22) **PCT Filed: Dec. 27, 2001**(86) **PCT No.: PCT/FR01/04212**

The invention concerns novel pharmaceutical compositions capable of comprising micelles containing at least a very lipophilic principle, enabling to enhance bioavailability of active principles insoluble in aqueous solvents called MIDDs® (Micellar Improved Drug Delivery Solutions).

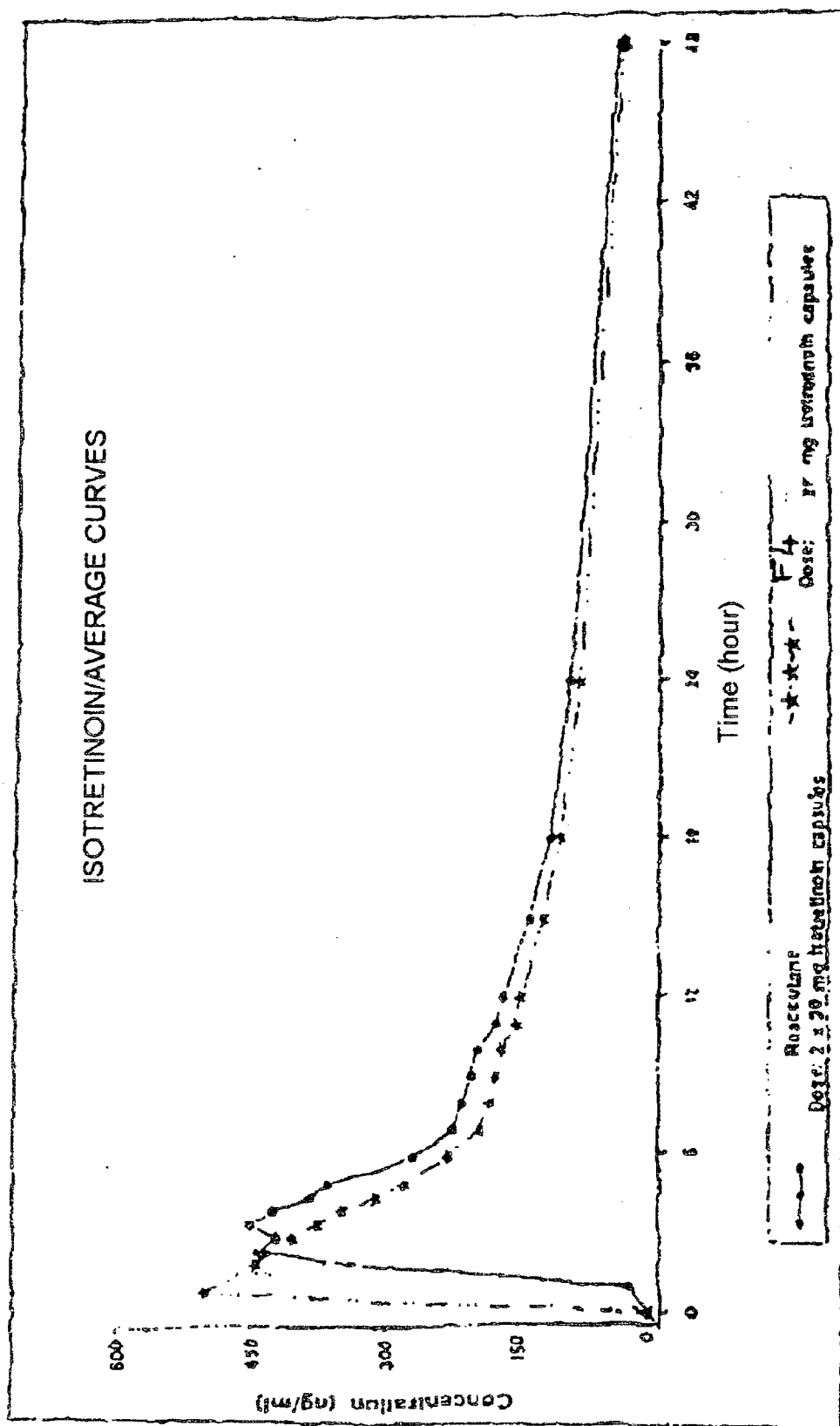


FIGURE 1

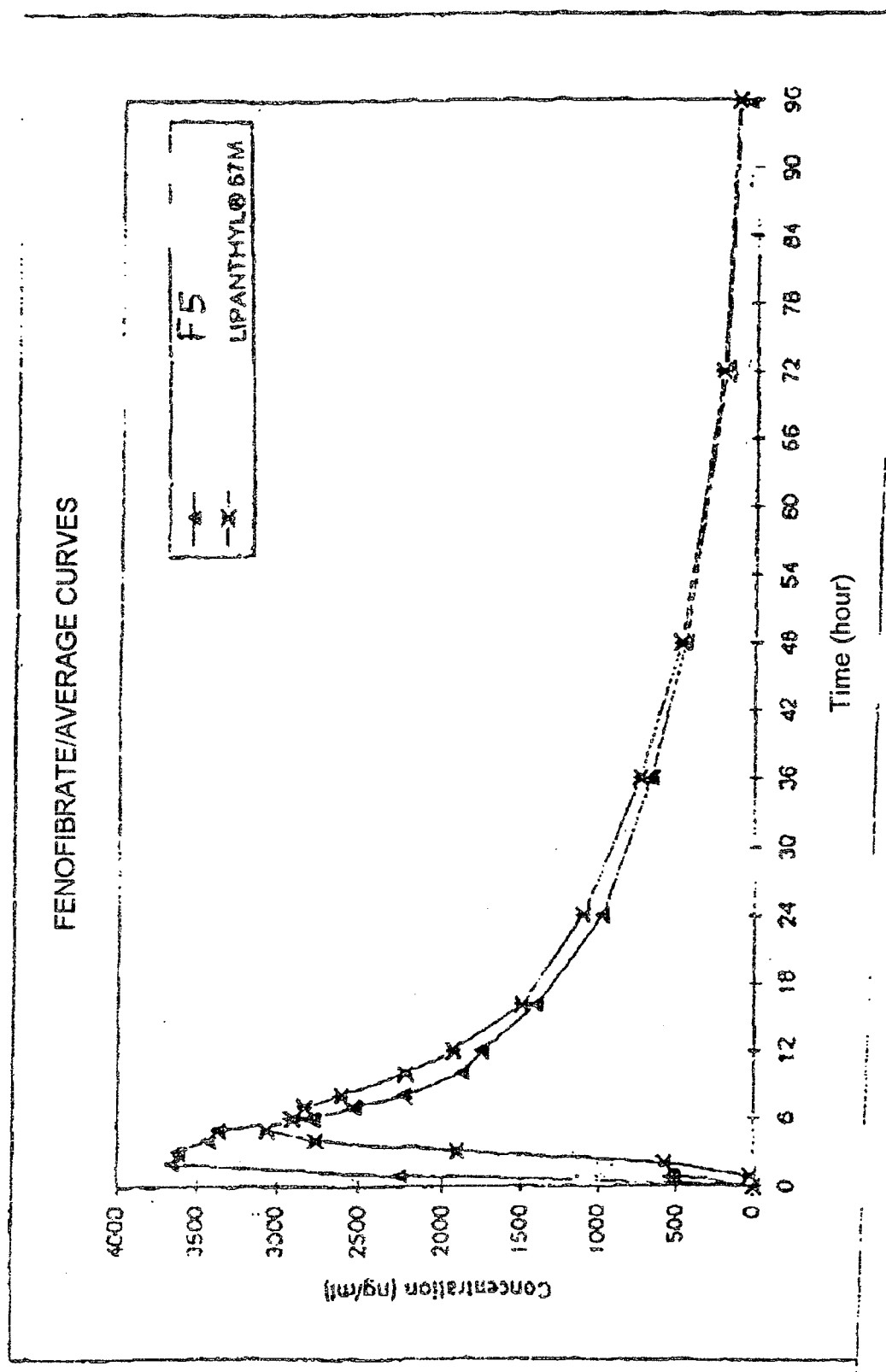


FIGURE 2

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MICELLAR COLLOIDAL PHARMACEUTICAL COMPOSITION CONTAINING A LIPOPHILIC ACTIVE PRINCIPLE

[0001] The present invention relates to novel micelle-forming pharmaceutical compositions containing at least one lipophilic active principle, which make it possible to increase the bioavailability of active principles insoluble in aqueous solvents, designated by the term MIDDs® (Micellar Improved Drug Delivery Solution).

[0002] This novel micelle-forming pharmaceutical dosage form is similar to known forms described as *Self Emulsifying Drug Delivery Systems* (SEDDS) or self-emulsifying systems, comprising a lipid phase and large quantities of surfactants (S) and/or of solvents. These self-emulsifying systems have been used for a long time in pharmaceutical preparations.

[0003] In the pharmaceutical industry, improving the bioavailability of very lipophilic active principles (AP) intended to be administered orally is of great interest to formulation pharmacists.

[0004] The formulation of lipophilic APs, and a fortiori that of very lipophilic APs, poses real problems mainly due to their low solubility in aqueous liquid pharmaceutical excipients, to their propensity to precipitate or to recrystallize from aqueous solution and to their low solubility in the fluids of the gastrointestinal tract from which they have to be absorbed.

[0005] Various techniques have already been proposed which are aimed at improving the solubilization of these lipophilic (hydrophobic) APs and their absorption from the digestive system, in order to increase the bioavailability thereof.

[0006] The improvement of the therapeutic efficacy of hydrophobic APs by virtue of their formulation as an oily solution or with the aid of their administration after a meal high in lipids has been exploited for several decades.

[0007] The bioavailability of an AP depends on its concentration in the gastrointestinal fluid; the latter itself depends on the release of the AP from the oily phase. The more lipophilic an AP, the less it tends to migrate in the digestive fluids. The absorption of these oily solutions starts by a hydrolysis at the oil-water interface, followed by a solubilization in the micelles of bile salts which penetrate into the intestinal microvilli, thus transporting the hydrophobic AP (NA Armstrong et al., *Int. J. Pharm.*, 1980, 6, 195-204).

[0008] The release of an AP from an oily formulation provided in appropriate gelatin capsules is common and numerous pharmaceutical preparations are marketed in this form.

[0009] Accordingly, French patent application FR-A-2 408 345 describes the preparation of micronized progesterone which is provided in the form of an oily suspension thereof, in particular based on vegetable oil (soybean lecithin, peanut oil, etc) in soft gelatin capsules. This proprietary product is marketed under the name Utrogestan®.

[0010] It is also known that the bioavailability of lipophilic APs can be increased by their formulation with the aid of digestible oils and hydrophilic and lipophilic surfactants

(K J McGREGOR et al., *Adv. Drug Deliv. Rev.*, 1997, 25, 33-46 and international application WO 95/24893). This type of formulation makes it possible to maintain the AP in solution during its passage into the digestive tract and until its intestinal absorption.

[0011] The digestion of oil ingredients of this type of formulations often has the advantage of solubilizing the AP in mixed micelles consisting of bile salts and products of lipolysis of the triglycerides of the digestible oil used.

[0012] However, the presence of surfactants can inhibit lipolysis, which requires the preliminary evaluation in vitro of the digestibility of the oils of a given formulation. Moreover, the quantities of digestible oils which should sometimes be used in order to avoid the recrystallization of the AP in vivo are too high to allow the manufacture of a marketable capsule.

[0013] It has, moreover, already been envisaged to optimize the lipid formulation of scarcely soluble APs using self-emulsifying vehicles capable of spontaneously forming a microemulsion upon contact with an aqueous phase in vitro and, likewise, at the level of the site of absorption in vivo.

[0014] These self-emulsifying preparations (*Self-Emulsifying Drug Delivery Systems*: SEDDS) are mixtures of oils and surfactants, which are isotropic, sometimes containing cosolvents and which self-emulsify with gentle stirring, a condition similar to the conditions encountered in the digestive tract (C W Pouton, *Int. J. Pharm.*, 1985, 27, 335-348; M G Wakerly et al., *Am. Chem. Soc. Symposium Series*, 1986, 311, 242-255; Charman et al., *Pharm. Res.*, 1992, 9, 87-93; B J Aungst, *J. Pharm. Sci.*, 1993, 82, 979-987; P Constantinides, *Pharm. Res.*, 1995, 12, 1561-1572).

[0015] The physical phenomena which explain the formation of microemulsions and the equilibria governing them have been widely studied and modelled (M Borkovec, *Adv. Colloid Interface Sci.*, 1992, 37, 195-217 and references cited).

[0016] Microemulsions find numerous applications in various fields. The study of the formulation of these transparent dispersions has allowed researchers interested by their physicochemical potentials (H L Rosano et al., *J. Colloid Interface Sci.*, 1979, 72, 233-244) or pharmaceutical potentials (C W Pouton, mentioned above, W A Ritschel et al., *Meth. Find. Exp. Clin. Pharmacol.*, 1990, 12, 127-134 and W A Ritschel, *Meth. Find. Exp. Clin. Pharmacol.*, 1991, 13, 205-220) to specify the relevant procedures and the appropriate methods for analyzing the performance of the so-called SEDDS self-emulsifying systems.

[0017] More particularly, patent application EP-A-0 670 715 describes SMEDDS® (*Self Micro-Emulsifying Drug Delivery System*) which contain a lipophilic active principle such as indometacin, diclofenac and hydrocortisone, a lipophilic phase preferably representing from 10 to 75% by weight of the total weight of the composition and consisting of a mixture of glycerides and C₈-C₁₈ fatty acid esters having a hydrophilic-lipophilic balance (HLB) of less than 16 and preferably of close to 14, a surfactant based on glycerides having an HLB of less than 16, a cosurfactant (CoS) chosen from lauryl esters of propylene glycol, oleyl esters of polyglycerol and ethyl diglycol, the S/CoS ratio being between 0.5 and 6. Upon contact with hydrophilic

phase, consisting for example of the physiological fluid of the intestinal medium, this composition spontaneously forms a microemulsion.

[0018] These microemulsifying systems make it possible to solubilize certain hydrophobic APs; however, they do not make it possible to systematically improve their bioavailability (Farah, self-microemulsifying drug delivery systems for improving in-vitro dissolution of drugs: AAPS Annual meeting Orlando, Fla., 1993).

[0019] Now, maintaining a lipophilic AP in micellar solution allowing its intestinal absorption is the key to success in preparing an effective lipid formulation.

[0020] Furthermore, the best SEDDSs, i.e. those which solubilize a large quantity of AP and which form very fine micellar dispersions, are generally the most hydrophilic. Now, it is for these hydrophilic SEDDSs (containing a hydrophilic S and CoS having high HLB values, in general greater than 12) that the risks of recrystallization of the AP in vivo are the greatest (Pouton, Bulletin Technique Gattefossé, 1999, 92, 41-49) and consequently the suprabioavailability of the AP is not necessarily achieved.

[0021] Indeed, while this type of self-micro emulsifying systems, which is described in patent application EP-A-0 670 715 (with a lipophilic phase having an HLB of close to 14), makes it possible to improve the formulation and the bioavailability of certain APs, it leads, on the other hand, with very lipophilic APs, to unstable lipid medicinal solutions and, for some extremely lipophilic active principles, this physical instability of the lipid medicinal solution is additionally coupled with the formation of unstable microemulsions upon contact with an aqueous phase, hence a failure of the pharmaceutical formulation.

[0022] Moreover, international application WO 96/21439 describes formulations based on a mixture of saturated polyglycolized C₈-C₁₈ glycerides having an HLB=14 (Gelucire®—company Gattefossé) and fenofibrate which is a lipophilic AP.

[0023] However, in order to be stable, these formulations require the presence of a cellulosic polymer so as to increase the viscosity thereof.

[0024] Finally, there has also already been proposed, in particular in international application WO 99/56727, the formulation of active principles which are slightly soluble in water by means of self-emulsifying compositions, of emulsions or of microemulsions containing from 5 to 70% of an oily component having an HLB of less than or equal to 4 and a surfactant system containing one or more surfactants having an HLB of between 10 and 20; these compositions being substantially free of hydrophilic solvent system.

[0025] While this type of compositions has improved stability properties given the absence of a hydrophilic solvent system, it is not satisfactory for solubilizing very lipophilic active principles.

[0026] The lipophilicity of an AP can be determined as a function of its coefficient of partition (P) between octanol and water which corresponds to the concentration of the AP in octanol (C_{Oct})/concentration of the AP in water (C_{Water}) ratio.

[0027] The determination of the partition coefficient is a factor which is widely exploited in various fields of appli-

cation of therapeutic or pharmacochemical chemistry, from the synthesis of chemical substances for medicinal use to the analysis of pharmaceutical products.

[0028] This characteristic is in particular taken into consideration by pharmacologists and toxicologists given the fundamental importance of the partition of medicinal active principles between biological media (in particular in terms of absorption and distribution) for the expression of their activity and/or their toxicity.

[0029] Thus, the determination of the octanol/water partition (P) coefficient, generally expressed as log P, is a major factor among the indicators of the structure-activity relationships for medicinal active principles or for toxic substances (C. Hansch et al., *Exploring QSAR*, (1995), Vol. I & II, Ed. American Chemical Society, USA; C. Hansch et al., *J. Pharm. Sci.*, 1987, 76, 663-687; V. Pliska et al., *Lipophilicity in drug action on toxicology*, Vol. 4 Verlagsgesellschaft mbH. Weinheim (1996); H. van de Waterbeemd, *Quantitative approaches to structure-activity relationships*, in: *The practice of medicinal chemistry*, Ed.: Wermuth, Academic Press, London (1996); Association Française des Enseignants de Chimie Thérapeutique: *Traité de Chimie Thérapeutique*, 7 volumes, Ed. TEC & DOC. Paris, (1992-2000).

[0030] When the P ratio is greater than 1, it means that C_{Oct} is greater than C_{Wat}, and that consequently the AP is lipophilic (log P>0). It is therefore possible to deduce therefrom that the higher the log P of an AP, the more pronounced the lipophilic character exhibited by it.

[0031] However, this physicochemical characteristic is not used in the field of galenic pharmacy (pharmaceutical formulation) and no prior art document makes reference to the notion of log P and really takes into account this criterion in the formulation strategy.

[0032] It is in order to overcome all these problems that the inventors have developed that which constitutes the subject of the invention.

[0033] The inventors set themselves the objective of providing a self-emulsifying pharmaceutical composition intended for oral administration, capable of forming a micellar solution or a microemulsion upon contact with digestive fluids, thus allowing the formulation of very lipophilic, or even extremely lipophilic, active principles while improving their bioavailability, said composition being stable in the liquid state and in the form of a microemulsion and leads to a very fine and homogeneous micellar dispersion.

[0034] For the purposes of the present invention, it is considered that the very lipophilic APs are those having a log P greater than 2, the extremely lipophilic APs having a log P greater than 4.

[0035] The subject of the present invention is therefore a self-micro emulsifying pharmaceutical composition for oral use comprising:

[0036] at least one lipophilic active principle,

[0037] at least one surfactant having a hydrophilic/lipophilic balance of less than 16,

[0038] at least one cosurfactant,

[0039] at least one lipophilic phase, characterized in that:

- [0040] the lipophilic active principle(s) have a log P greater than 2,
- [0041] the surfactant(s) represent at least 50% by weight of the total weight of said composition,
- [0042] the cosurfactant(s) are chosen from the good solvents for said active principle(s),
- [0043] the lipophilic phase is optionally surface-active and represents from 0.5 to 4.5% of the total weight of said composition and has an HLB of less than or equal to 6, and
- [0044] when the active principle is different from a retinoid, then said composition additionally comprises a nonsurfactant oily phase representing from 1 to 12% of the total weight of said composition.
- [0045] The pharmaceutical composition in accordance with the invention is essentially distinguishable from those described by the prior art by the fact that the lipophilic phase and the oily phase have very low HLB values and are used in small quantities and also by the essential presence of a CoS which has a role of good solvent for the AP in the pharmaceutical dosage form.
- [0046] The inventors have indeed demonstrated that this composition allows the dissolution of very lipophilic APs and leads, in the presence of a hydrophilic phase, to formulations forming fine, stable and homogeneous micellar colloidal dispersions, thus making it possible to improve the bioavailability of these APs in the gastrointestinal tract.
- [0047] The pharmaceutical composition in accordance with the invention makes it possible in particular to obtain microemulsions whose micelles have a size of less than 500 nm and more particularly of between 1 and 200 nm.
- [0048] Depending on the excipients used in their formulation, there may be liquid lipid solutions or solid (semisolid, pasty) solutions at room temperature. The pharmaceutical compositions in accordance with the present invention form in all cases a microemulsion or a colloidal solution, of the micellar type, upon contact with an aqueous phase.
- [0049] All the APs having a log P greater than 2, and more particularly greater than 4, may be used in accordance with the present invention.
- [0050] These very lipophilic, or even extremely lipophilic, active principles are generally molecules having long carbon chains and/or aromatic rings or nuclei carrying hydrophobic substituents, with very few hydrophilic groups or substituents.
- [0051] These very lipophilic active principles may be chosen in particular from retinoids, hypolipidemic agents, steroid hormones, steroid anti-inflammatories, nonsteroid anti-inflammatories (NSAIDs), antiretrovirals, protease inhibitors ("navirs"), antiacids, proton pump inhibitors, antiemetics, fat-soluble vitamins, cardiovascular system drugs, platelet aggregation inhibitors, cancer drugs, certain plant extracts and their isolated or derived APs, immunosuppressants, central nervous system drugs, antimigraines, antibiotics, antifungals and antiparasitics, provided of course that they have a log P greater than 2.

[0052] Retinoids are compounds capable of binding and interacting with a retinoic acid receptor (alpha, beta or gamma RAR) or with a retinoid X receptor (alpha, beta, gamma RXR). As examples of such retinoids, there may be mentioned, firstly, the retinoids derived from vitamin A such as tretinoin, also known by the name of all-trans-retinoic acid or all-trans-vitamin A acid, isotretinoin which corresponds to the 13-cis isomer of tretinoin, and which, as a result, is also called 13-cis-retinoic acid or 13-cis vitamin A acid, 9-cis-retinoic acid or 9-cis vitamin A acid, acitretin, etretinate, but also the acetylene retinoids such as tazarotene, the retinoids derived from naphthalene such as lonapalene and 2-(5,6,8-tetrahydromethyl-2-anthryl)-4-thiophenecarboxylic acid, and the retinoids containing an adamantyl ring such as adapalene, 6-[3-(1-adamantyl)-4-hydroxyphenyl]-2-naphthoic acid and 4-[3-(1-adamantyl)-4-methoxybenzamido]benzoic acid and their esters.

[0053] Among these retinoids, the use of isotretinoin (log P=6) is particularly preferred according to the invention.

[0054] As hypolipidemic agents, which are compounds capable of inhibiting the synthesis of cholesterol and triglycerides, there may be mentioned, in particular, fibrates such as 1-methylethyl ester of 2-(4-(4-chlorobenzoyl)phenoxy)-2-methylpropanoic acid also called fenofibrate (log P=5.24) and related products of fibrate class such as clofibrate (log P=3.65), bezafibrate (log P=3.53), ciprofibrate (log P=3.15) and gemfibrozil (log P=3.90).

[0055] There may also be mentioned, among the other hypolipidemic agents, bishioethers, including probucol and tiadenol (log P=4.58), the class of HMG Co-A reductase inhibitors (statins) such as for example simvastatin (log P=4.68), mevastatin (log P=3.52), lovastatin (log P=4.04), atorvastatin, pravastatin, fluvastatin, cerivastatin, and the class of ACAT inhibitors such as melinamide and its structural analogs.

[0056] As steroid hormones, there may be mentioned in particular estrogens which are estradiol derivatives and esters of (log P>5), progesterone (log P=3.87), danazol (log P=4.53), testosterone (log P=3.32) and esters and derivatives of testosterone (log P>4). There may also be mentioned antiandrogens including flutamide (log P=3.5), nilutamide; 5 α -reductase inhibitors, competitive inhibitors of testosterone such as finasteride (log P=3.03); quinazoline derivatives such as alfuzosin; nonsteroid agonists/antagonists of the estrogen receptors such as tamoxifen (log P=4.03) and raloxifen.

[0057] As steroid anti-inflammatories, there may be mentioned in particular glucocorticoids having a log P of between 2 and 3 such as prednisolone, cortisone, its esters and derivatives (log P=2.1 to 2.4).

[0058] As NSAIDs, there may be mentioned in particular mefenamic acid (log P=5.3), naproxen (log P=2.90), nabumetone (log P=3.32), ibuprofen (log P=3.50 to 4.50) and COX-2 inhibitors such as celecoxib, rofecoxib, parecoxib and valdecoxib.

[0059] Antiretrovirals and protease inhibitors are compounds which are sparingly soluble in water, whose partition coefficients can be calculated or determined by the analytical route, among which there may be mentioned amprenavir (solubility 0.04 mg/l), saquinavir and saquinavir mesylate (solubility 2.22 mg/ml) and ritonavir (almost insoluble in water).

[0060] As antacids and proton pump inhibitors, there may be mentioned in particular omeprazole (log P=2.23), pantoprazole, rabeprazole (or pariprazole), lansoprazole and timoprazole.

[0061] As antiemetics, there may be mentioned in particular domperidone (log P=4.05), serotonin antagonists ("serotons") such as ondansetron (log P=2.63), granisetron and azasetron.

[0062] As fat-soluble vitamins, there may be mentioned in particular vitamins A or retinol (log P=5.68), D including calcitriol, E or tocopherols, K or menadione (log P=8).

[0063] Among the cardiovascular system drugs, there may be mentioned in particular antagonists of angiotensin II (sartans) such as valsartan, losartan, irbesartan, candesartan, tasosartan, telmisartan (log P=4.8); α - and β -blockers such as carvediol, celiprolol (log P=2.07); calcium inhibitors (dihydropyridines) such as verapamil (log P=3.8), diltiazem (log P=2.7), nifedipine (log P=2.75) and nitrendipine (log P=3.7). It is also possible to mention other compounds, antihypertensives, such as renin-inhibiting peptides, oxazolidinone derivatives or glycol peptides substituted with amino residues and/or azole- or thiazole-containing heterocyclic rings (log P of between 2 and 4).

[0064] As platelet aggregation inhibitors, there may be mentioned in particular clopidogrel (oil), ticlopidine; coumarinic anticoagulants including warfarin (log P=2.70) and compounds of the indanedione group, including phenyl indanedione (log P=2.90).

[0065] As cancer drugs, there may be mentioned in particular paclitaxel and docetaxel which are compounds which are insoluble in water; *Vinca minor* extracts and alkaloids such as vincristine (log P=2.80), vincalkebblastin or vinblastin (log P=3.69), vincamine and their derivatives; *Ochrosia elliptica* alkaloids including ellipticine (log P=4.80).

[0066] Among the plant extracts and their isolated or derived APs, there may be mentioned in particular alkaloids such as yohimbine (log P=2.73), flavonoids including diosmin, rutin and its derivatives such as troxerutin; *Pygeum africanum* or *Serenoa repens* extracts.

[0067] As immunosuppressants, there may be mentioned in particular ciclosporin (log P=2.92) and tacrolimus.

[0068] Among the various central nervous system drugs are tranquilizers, sedatives, hypnotics and anesthetics. By way of example, there may be mentioned barbiturates (log P of between 2 and 2.5) such as thiobarbiturates (log P of close to 3); anxiolytics such as benzodiazepines (log P of between 2 and 3); antihistamines (log P of between 2 and 5) such as terfenadine (log P=3.22), loratadine (log P=5.20), desloratadine and cetirizine; tricyclic and serotoninergic antidepressants such as fluoxetine, paroxetine, sertraline and citalopram.

[0069] As antimigraines, there may be mentioned compounds of the serotoninergic "triptans" group such as oxitriptan, sumatriptan and almotriptan.

[0070] Among the antibiotics, there may be mentioned in particular third generation cephalosporins such as cefixim trihydrate and cefpodoxim proxetil; macrolides such as azithromycin, clarithromycin, roxithromycin (log P of close

to 2.5), josamycin (log P=2.39), spiramycin; synergists such as pristinamycin, quinolones and quinoxalines, including carbadox.

[0071] Among the antifungals, there may be mentioned in particular griseofulvin (log P=2.18), amphotericin B, terbinafin (log P=5.42) and azole-containing antifungals (conazoles) including miconazole (log P=2.3 and 5.6), itraconazole (log P=5.68), ketoconazole (log P=4.34) and fluconazole.

[0072] Among the antiparasitics, there may be mentioned antimalarials such as halofantrine (log P=8.2), mefloquin (log P=3.36), proguanil (log P=2.53), pyrimethamine (log P=2.69), extracts of *Artemisia* spp and substances isolated from these extracts and their derivatives such as artemisin, artemisinin and their derivatives (log P=2.2 to 4); the avermectin series, including ivermectin which is practically insoluble in water (partition coefficient chloroform/water: log P=3; partition coefficient ethyl acetate/water: log P=4); anthelmintics derived from benzimidazole for veterinary use such as for example tiabendazole (log P=2.31), albendazole (log P=3.22), mebendazole (log P=3.10), fenbendazole (log P=4.26) and triclabendazole (log P=6.45); the class of salicylanilides for veterinary use, used in fascioloses (dovicides) and other parasitoses comprising in particular bromoxanide (log P=5.65), brotianide (log P=5.30), clioxanide (log P=5.45), closantel (log P>7), oxyclozanide (log P=5.35), rafoxanide (log P=8.75) and dibromosalan (log P=5.18) and tribromosalan (log P=5.86).

[0073] According to the invention, the active principle(s) are preferably chosen from retinoides, hypolipidemic agents and steroid hormones.

[0074] According to the invention, the active principle(s) having a log P greater than 2 preferably represent from 1 to 10% by weight relative to the total weight of the composition.

[0075] In the particular case of retinoides, and still more particularly in the case of isotretinoin, this quantity preferably varies between 1 and 2.5% by weight relative to the total weight of the composition. Thus, as seen above, when the pharmaceutical composition in accordance with the invention contains a retinoide, then the presence of an oily phase, although possible, is nevertheless not essential.

[0076] In the particular case of hypolipidemic agents, and still more particularly in the case of fenofibrate, this quantity preferably varies between 5 and 10% by weight relative to the total weight of the composition.

[0077] In the particular case of steroid hormones, and still more particularly in the case of progesterone, this quantity preferably varies between 3 and 7% by weight relative to the total weight of the composition.

[0078] Among the surfactants having an HLB of less than 16, there may be mentioned in particular the surfactants which behave as good solvents for the AP to be formulated, among which are polyglycolized C₈-C₁₈ glycerides, in other words macrogol glycerides of C₈-C₁₀ chain fatty acids, such as caprylocapric macrogol glycerides such as for example the mixture of mono-, di- and triglycerides and of mono- and diesters of polyethylene glycol marketed under the trademark Labrasol® (HLB=14) by the company Gattefosse, and the oleic esters of polyglycerol having an HLB=10 such as

for example the product marketed under the trademark Plurol® oleic by the company Gattefosse or the mixture of polyglycolized glycerides of C₈-C₁₈ fatty acids marketed under the trademark Gelucire® by Gattefosse, including Gelucire 44/14, or lauric macrogol glycerides. There may also be mentioned polysorbates, in other words sorbimacrogol—or polyethylene glycols (PEG)-esters of C₁₂-C₁₈ fatty acids such as hydrogenated ricinoleic, stearic, palmitic, oleic and lauric acids and their derivatives, marketed under the trademarks Ablunol® (Taiwan Surf), Aldospense® (Lonza), Arlacel® (ICI), Crillet® (Croda), Drewmulse® (Stepan Food Ingredients), Ethylan® (Akcros), Emulpharma® (Respharma), Eumulgin® (Henkel), Montanox® (Seppic), Nikkol® (Nikko Chem. Co), Nissan Nonion® (Nippon Oils & Fats), Sorbilene® (Auschem), Sorgen® TW (Dai-ichi Kogyo Seiyaku) and Tween® (BASF); macrogol and propylene glycol esters of C₈-C₁₈ fatty acids (hydrogenated ricinoleic, stearic, capric, caprylic), marketed under the trademarks Captex® (Hüls), Cremophor® (BASF), Drewmulse® (Stepan Food Ingredients), DUB CAPS and DUB 810 (Stéarineries Dubois), Eumulgin® (Henkel) and Tagat (Goldschmidt); the macrogol-glyceride esters of C₁₂-C₁₈ fatty acids (hydrogenated ricinoleic, stearic, palmitic, oleic, lauric), marketed under the trademarks Akolip® (Karlshamns), Capmul® (Abitec), Cremophor® (BASF), Emulpharma® (Respharma), Ethylan® (Akcros), Eumulgin® (Henkel), Etocas® (Croda), Myrj® (ICI), Nikkol® (Nikko Chem. Co) and Tagat® (Goldschmidt); the polyglyceric esters of C₁₂-C₁₈ fatty acids (isostearic, lauric, oleic or stearic), marketed under the trademarks Caprol® (Abitec), Drewpol® (Stepan Food Ingredients) and Nikkol Decaglyn® (Nikko Chem. Co); and mixtures thereof.

[0079] These surfactants represent at least 50% and preferably from 70 to 85% of the total weight of the composition.

[0080] For the purposes of the present invention, a cosurfactant is considered as a good solvent for the active principle(s) present in the pharmaceutical composition in accordance with the invention, when it makes it possible, during dissolution trials, to solubilize enough active principle(s) while being compatible with the formulation of the finished product. For example, isotretinoin is 3% soluble in monoethyl ether of diethylene glycol (marketed under the trademark Transcutol® by Gattefosse; fenofibrate is 5% soluble in the same solvent; progesterone is 5% soluble in propylene glycol monocaprylate (marketed under the trademark Capryol by Gattefosse).

[0081] In accordance with the invention, the Ss and the CoSs are preferably nonionic compounds.

[0082] Among the CoSs which can be used in the pharmaceutical composition in accordance with the invention, there are preferably used the CoSs which behave as good solvents for the AP to be formulated and among which there may be mentioned in particular monoethyl ether of diethylene glycol (MEDG) corresponding, for example, to the product sold under the trademark Transcutol® by the company Gattefosse. There may also be mentioned the CoSs involved as solvent for the AP to be formulated, such as N-methyl-2-pyrrolidone or Pharnasolve® (ISP), the triester of glycerol and acetic acid or Triacetin® (Aldrich), dimethyl isosorbate (Aldrich), polyethylene glycols (PEG) such as PEG-400 and PEG-600 (in other words PEG-8 and PEG-12)

and the products marketed for example under the names Carbowax® (Union Carbide), Lipoxol® (Hüls), Pluracol® (BASF), and the alcohols and glycols used as solvents or cosolvents, ethanol, isopropanol, glycerol, propylene glycol, butylene glycol, glycofurol and sorbitol; mono- and diesters of propylene glycol and of caprylic, capric and lauric fatty acids, marketed under the trademarks Labrafac® PG, Capryol® and Lauroglycol® (Gattefosse); mono- and diglycerides of caprylic, capric, lauric, oleic, stearic fatty acids marketed under the trademarks Akoline® (Karlshamns), Capmul® (Abitec), Drewmulse® (Stepan Food Ingredients), DUB GMS (Stéarineries Dubois), Imwitor® (Hüls), Maisine® and Peceol® (Gattefosse); and mixtures thereof.

[0083] These CoSs preferably represent from 5% to 20% by weight relative to the total weight of the composition.

[0084] When the pharmaceutical composition in accordance with the invention contains a retinoid, and in particular isotretinoin, as AP, then the CoS concentration is more preferably between 10 and 15% by weight relative to the total weight of the composition.

[0085] When the pharmaceutical composition in accordance with the invention contains a hypolipidemic agent such as fenofibrate, as AP, then the CoS concentration is more preferably between 5 and 10% by weight relative to the total weight of the composition.

[0086] According to the invention, the lipophilic phase preferably has an HLB of less than or equal to 4, is liquid at room temperature and is preferably chosen from fatty acid esters, in particular macrogol (or polyethylene glycol) glycerides, in other words polyglycolized glycerides of fatty acids such as for example PEG-6 glyceryl monooleate having an HLB=3 sold under the trademark Labrafil® M 1944 CS by the company Gattefosse, PEG-6 glyceryl linoleate having an HLB=4 sold under the trademark Labrafil® M 2125 CS by the company Gattefosse; sorbitan esters of saturated or unsaturated fatty acids such as lauric, oleic, stearic, palmitic, sesquioleic acids and their derivatives, marketed under the trademarks Arlacel® (ICI), Crill® (Croda), Drewmulse® (Stepan Food Ingredients), Ethylan® (Akcros), Glycomul® (Lonza), Kemester® (Witco Oleo-Surf), Montane® (Seppic), Nikkol® (Nikko Chem Co), Nissan Nonion® (Nippon Oils & Fats), Sorbirol® (Auschem), Sorgen® TW (Dai-ichi Kogyo Seiyaku) and Span (ICI); glycerol, propylene or butylene glycol esters of fatty acids marketed under the trademarks Arlacel® (ICI), Capmul® (Abitec), Drewmulse® (Stepan Food Ingredients), DUB GMS (Stéarineries Dubois), Imwitor® and Miglyol® (Hüls), Maisine®, Olicine® and Peceol® (Gattefosse); medium chain triglycerides of caprylic, capric and lauric fatty acids such as the products marketed under the trademarks Akomed® (Karlshamns), Captex® (Abitec), Crodamol® (Croda), DUB MCT (Stéarineries Dubois), Imwitor® and Miglyol® (Hüls), Labrafac® CC (Gattefosse), Neobee® (Stepan Food Ingredients); and mixtures thereof.

[0087] According to a preferred embodiment of the invention, and when the AP is a retinoid such as isotretinoin, then the pharmaceutical composition contains a lipophilic phase in a proportion preferably of between 3 and 4.5% by weight relative to the total weight of the composition.

[0088] The oily phase may be chosen from oils of natural and synthetic origin.

[0089] Among the oils of natural origin, there may be mentioned in particular almond, peanut, rapeseed, cotton seed, linseed, corn, olive, borage, evening primrose, fish, palm, palm kernel, grapeseed, sesame, soybean and sunflower oils, and the like. These oils may be from the first pressing, refined or interesterified, such as the oils marketed under the trademarks Akofine®, Akosoft®, Akosol® (Karlsbams), Myverol®, Myvacet® (Eastman) and Neobee® (Stepan Food Ingredients).

[0090] Among the oils of synthetic origin, the oils having an HLB value of less than or equal to 5, and still more particularly of less than or equal to 3, are preferred, among which there may be mentioned in particular the products marketed under the trademarks Captex® (Abitec), Crodamol® (Croda), DUB 810 PG (Stéarineries Dubois), Neobee® (Stepan Food Ingredients) and Labrafac® (Gattefosse).

[0091] When the oily phase consists of a synthetic oil, it may, according to the invention, have a very low HLB, of the order of 1 to 3, preferably chosen from the fatty acid esters sold under the name Labrafac®, such as Labrafac® PG, Labrafac® CC or Labrafac® lipophilic (Gattefosse), and mixtures thereof.

[0092] According to a preferred embodiment of the invention, and when the AP is a hypolipidemic agent such as fenofibrate, then the pharmaceutical composition contains an oily phase in a proportion preferably of between 2 and 12% by weight.

[0093] In the case where the composition requires it, it may prove useful to incorporate preservatives either into the lipid solution or into the envelope of the capsule such as for example: butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), group E vitamins or tocopherols, ethylenediaminetetraacetic acid (EDTA) or its salts, methyl- or propylparabens, salts of para-hydroxybenzoic acid derivatives, etc.

[0094] According to an advantageous embodiment of the invention and when the pharmaceutical composition contains a retinoid, and in particular isotretinoin, then the composition contains at least one group E vitamin, preferably vitamin E.

[0095] The presence of vitamin E is indeed advantageous insofar as, in addition to its antioxidant effect toward isotretinoin, it also makes it possible to avoid the formation of crystals during storage of the compositions in accordance with the invention at low temperature.

[0096] The pharmaceutical composition in accordance with the invention may also contain one or more thickeners chosen from celluloses, waxes, acrylic polymers and gums. This thickening agent is preferably chosen from celluloses such as carboxymethylcellulose, hydroxypropylmethylcellulose, hydroxymethylcellulose and methylcellulose.

[0097] As thickening agents, there may also be used the surfactants described above, in particular esters of fatty acids and of polyethylene glycol.

[0098] According to an advantageous embodiment of the invention, and when the pharmaceutical composition contains a retinoid such as isotretinoin, then it also preferably contains at least one thickening agent.

[0099] The pharmaceutical composition in accordance with the invention may be packaged in hard gelatin capsules or soft gelatin capsules, for example made of gelatin, which, after ingestion orally and disintegration, will release the pharmaceutical composition in accordance with the invention which will spontaneously form a microemulsion upon contact with physiological fluid.

[0100] The pharmaceutical compositions in accordance with the invention may be prepared according to a method consisting:

[0101] in a first step, of dissolving the AP to be formulated in its appropriate solvent which is the CoS, optionally in the presence of a cosolvent or a surfactant or of the lipophilic phase and optionally of the oily phase when it is present;

[0102] and then in a second step, of incorporating this solution, with stirring and/or homogenization, into the liquid or liquefied surfactant, in which case the oily phase may be mixed beforehand, according to one variant of this same method, at a temperature which makes it possible to obtain a homogeneous solution, and then

[0103] in a third step, after returning to room temperature, of distributing the solution thus obtained into hard gelatin capsules or soft gelatin capsules, the quantity of solution incorporated being calculated according to the required unit dose of AP.

[0104] In addition to the preceding features, the invention further comprises other features which will emerge from the description which follows, which refers to an example relating to a comparative study of the stability of a composition in accordance with the invention compared with a composition as described in the prior art, to an example relating to a comparative study of the permeability of Caco-2 cells to isotretinoin in various formulations, to an example relating to the study of the bioavailability of the isotretinoin formulated in accordance with the invention compared with the commercial presentation ROACCUTANE®, to an example of a formulation based on fenofibrate, to an example relating to the study of the bioavailability of the fenofibrate formulated in accordance with the invention compared with the commercial presentation LIPANTHYL® 67M, to an example of a formulation based on progesterone, and to the accompanying FIGS. 1 and 2 in which:

[0105] FIG. 1 represents the bioavailability of the isotretinoin formulated in accordance with the invention compared with that of the commercial product ROACCUTANE®;

[0106] FIG. 2 represents the bioavailability of the fenofibrate formulated in accordance with the invention compared with that of the commercial product LIPANTHYL® 67M.

[0107] It should be clearly understood however that these examples are given solely by way of illustration of the subject of the invention, and do not constitute in any manner a limitation thereto.

EXAMPLE 1

Comparative Study of the Stability and Homogeneity of Compositions Based on Isotretinoin

[0108] 1) Pharmaceutical Compositions Prepared

[0109] Two pharmaceutical compositions based on isotretinoin containing the ingredients presented in Table I below were prepared, the percentages indicated are by weight:

TABLE I

Composition	F1 in accordance with the invention	F2 not forming part of the invention
Isotretinoin	1.4%	1.4%
Surfactant	Labrasol® (HLB = 14): 81%	Labrasol® (HLB = 14): 9.7%
Cosurfactant	Transcutol®: 13.6%	Capryol® (HLB = 5): 13.9%
Lipophilic phase	Labrafil® M 1944 CS (HLB = 3): 4%	Gelucire® 44/14 (HLB = 14): 75%

[0110] The CAPRYOL® used in the composition F2 is a propylene glycol monocaprylate containing 60% of monoesters.

[0111] 2) Study of the Stability and Homogeneity of the Compositions F1 and F2

[0112] It was observed that the composition F1 in accordance with the invention, that is to say containing less than 5% of a lipophilic phase having a low HLB, was liquid at room temperature and led, in the presence of a hydrophilic phase, to the formation of a fine microemulsion (120 nm), which was stable at 25° C., which is a temperature which discriminates in relation to the constituents of the self-emulsifying system, and which was homogeneous.

[0113] On the other hand, the composition F2 not forming part of the invention, because it contains a large quantity of lipophilic phase (75%) and having a high HLB (HLB=14), leads to a semisolid formulation at room temperature, which is unstable and leads, in the presence of a hydrophilic phase, to a nonhomogeneous micellar solution in the form of microdroplets, composed of two different populations of micelles in terms of size: on average 112 nm (33%) and 900 nm (67%).

EXAMPLE 2

Comparative Study of the Permeability to Isotretinoin as a Function of its Formulation

[0114] In order to carry out this study, the pharmaceutical composition F1 in accordance with the invention and as prepared above in Example 1 was compared with a composition F3 consisting of a solution of isotretinoin alone, at 1.4% in dimethyl sulfoxide (DMSO), and to the commercial formulation of isotretinoin sold under the trademark ROACCUTANE® containing isotretinoin in a mixture of excipients composed of yellow beeswax, hydrogenated and non-hydrogenated soybean oils, and partially hydrogenated vegetable oil.

[0115] The permeability study was carried out on intestinal epithelial cells Caco-2, according to the modalities

described in the articles by I J Hidalgo et al., "Characterization of the human colon carcinoma cell line (Caco-2) as a model system for intestinal epithelial permeability", Gastroenterology, 1989, 96, 736-749 and P Artursson et al., "Correlation between oral drug absorption in humans and apparent drug permeability coefficients in human intestinal epithelial (Caco-2) cells", Biochem. Biophys. Res. Commun., 1991, 175, 880-885.

[0116] Indeed, the intestinal absorption may be studied in vitro by means of differentiated cell cultures.

[0117] The intestinal cell line Caco-2 (derived from human colorectal carcinoma) develops the morphological characteristics of normal enterocytes (columnar epithelium of the wall of the small intestine).

[0118] When they are cultured on polycarbonate membrane, the Caco-2 cells form a monocellular layer of polarized enterocytes.

[0119] They are characterized as a representative model of the transport system of the epithelium of the small intestine, and from a morphological point of view and in terms of permeability toward solutes which are not the subject of a membrane permeation (I J Hidalgo et al., cited above).

[0120] The study of the passive absorption of AP across the intestinal epithelium, using the Caco-2 model, was validated with the aid of various APs.

[0121] This made it possible to establish a correlation between their absorption per os and the calculated apparent coefficient of permeability using the Caco-2 cellular model (P Artursson et al., cited above).

[0122] The membrane integrity of the Caco-2 cells was also studied. This integrity was monitored by virtue of the incorporation, into the working solution, of a carbon 14-labeled mannitol solution.

[0123] Thus, this tracer makes it possible to verify that the passage across the membrane and not outside went well. Indeed, the permeability to mannitol for all the solutions tested is comparable to the control permeability for mannitol.

[0124] The results obtained are presented in Table II below:

TABLE II

Compositions	F1 in accordance with the invention	F3 (solution of isotretinoin alone)	ROACCUTANE®
Permeability to isotretinoin (10 ⁻⁶ cm/s)	2.14	3.79	<0.1
Integrity of the membrane	preserved	preserved	preserved

[0125] These results show that the membrane integrity was preserved for all the compounds tested.

[0126] They also show that the pharmaceutical composition F1, in accordance with the invention, makes it possible to increase the permeability of the Caco-2 cells to isotretinoin and, consequently, the bioavailability of this active principle.

[0127] The good results of permeability of the composition F3 containing isotretinoin alone is explained by the fact that this active principle was completely dissolved in DMSO; however, this excellent solvent for organic substances cannot be used as it is in pharmaceutical preparations for toxicity considerations.

EXAMPLE 3

Comparative Study of the Bioavailability of Isotretinoin as a Function of its Formulation

[0128] In order to carry out this study, the following pharmaceutical composition F4 in accordance with the invention was prepared:

Active principle: isotretinoin	2%
S: Labrasol ® (HLB = 14)	80.5%
Co-S: Transcutol ®	13.5%
Lipophilic phase: Labrafil ® M1944 (HLB = 3)	4%

[0129] This pharmaceutical composition F4 was packaged in hard gelatin capsules each containing 9 mg of isotretinoin.

[0130] The bioavailability study was carried out according to a protocol for administering a single dose of each of the treatments: the test formula and the reference formula are administered according to a criss-cross and randomized order.

[0131] The isotretinoin formulated according to the pharmaceutical composition F4 was compared with that of the commercial formulation of isotretinoin sold under the trademark ROACCUTANE® and as described above in Example 2.

[0132] In order to observe the customary mode of administration and dosage of the reference proprietary product ROACCUTANE®, the two products were administered, during meals, at the rate of the single dose of 3 soft gelatin capsules of the composition F4 and two soft gelatin capsules of ROACCUTANE® at 20 mg.

[0133] The results obtained are presented in FIG. 1 which correspond to the plasma concentration of isotretinoin in ng/ml as a function of the time in hour.

[0134] At equal doses of AP isotretinoin, these results show a suprabioavailability of 37.5% for the composition F4, in terms of intensity of absorption, according to the comparative results of the areas under the total plasma concentration curves (AUC) and the plasma concentration peaks C_{max} (result greater than 48%, with in particular a lower variability of the pharmacokinetic response in the case of the composition F4).

[0135] These results also demonstrate a bioequivalence between the administered dose of 27 mg of isotretinoin (composition F4 in accordance with the invention) and the dose which is nevertheless greater than 40 mg of isotretinoin of ROACCUTANE®.

[0136] In terms of rate of absorption, these results also show that the composition F4 in accordance with the invention is more rapid than the reference composition ROACCUTANE®, with an earlier plasma concentration peak,

expressed by the parameter T_{max} , which is one hour on average for the composition F4, against 3 hours on average for ROACCUTANE®.

EXAMPLE 4

Pharmaceutical Composition Based on Fenofibrate

[0137] The following pharmaceutical composition F5, in accordance with the invention, was prepared:

Active principle: fenofibrate	8.1%
S: Labrasol ® (HLB = 14)	74.0%
Co-S: Transcutol ®	6.25%
Lipophilic phase: Labrafil ® M1944	0.8%
Oily phase: Labrafac ® PG (HLB = 1)	6.25%
Oily phase: Labrafac ® CC (HLB = 1)	4.6%

[0138] In the presence of an aqueous phase, this composition spontaneously led to a stable and fine microemulsion in which the fenofibrate was perfectly dissolved.

EXAMPLE 5

Comparative Study of the Bioavailability of Fenofibrate as a Function of its Formulation

[0139] This study was carried out under the same conditions as those described above in Example 3, in order to compare the bioavailability of the fenofibrate formulated in accordance with the invention (composition F5 as described above in Example 4) to the commercial fenofibrate formulation (micronized form) sold under the trademark LIPANTHYL® 67M.

[0140] The composition F5 was packaged in hard gelatin capsules each containing 66 mg of fenofibrate.

[0141] The composition F5 and LIPANTHYL® was administered during a meal at the rate of 1 hard gelatin capsule.

[0142] The results obtained are presented in FIG. 2, which correspond to the plasma concentration of fenofibric acid in ng/ml as a function of the time in hour.

[0143] In terms of rate of absorption, the composition F5 is more rapid than LIPANTHYL®, with an earlier plasma concentration peak, expressed by the parameter T_{max} , which is 2.5 hours on average for the composition F5 against 5.83 hours on average for LIPANTHYL®.

[0144] This bioequivalence between the composition F5 and the dose of 67 mg of the formulation LIPANTHYL® is particularly advantageous insofar as the composition F5 is found to be bioequivalent to the formulation LIPANTHYL®, which is itself suprabioavailable compared to the previously marketed nonmicronized form.

[0145] Consequently, the self-emulsifying and micelle-forming composition F5 in accordance with the invention makes it possible to obtain the maximum bioavailability of the fenofibrate while applying to this active principle a galenic route of preparation which is completely different from micronization, whereas, up until now, only the micronization of fenofibrate had made it possible to improve its bioavailability.

EXAMPLE 6

Pharmaceutical Composition Based on Progesterone

[0146] The following pharmaceutical composition F6 in accordance with the invention was prepared:

Active principle: Progesterone	5%
S: Labrasol® (HLB = 14)	8.5%
S: Gelucire® 44/14 (HLB = 14)	65%
Co-S: Capryol® PGMC (HLB = 5 to 6)	17.5%
Lipophilic phase: Labrafil® M1944	2%
Oily phase: Labrafil® CC (HLB = 1)	2%

[0147] This composition is essentially distinguishable from the prior art composition F2, which is not stable after a few months, by the fact that it contains 4% of oily phase. It spontaneously leads, in the presence of an aqueous phase, to a stable and fine microemulsion in which the progesterone is perfectly dissolved.

[0148] Indeed, it should be noted that the lipophilicity of the AP plays an important role in the equilibrium of the system. The addition of the oily phase makes it possible to better solubilize the progesterone and it is this oil which will be micellized and which makes it possible to significantly improve the stability.

1. A self-micro emulsifying pharmaceutical composition for oral use comprising:

- at least one lipophilic active principle,
- at least one surfactant having a hydrophilic/lipophilic balance of less than 16,
- at least one cosurfactant,
- at least one lipophilic phase, characterized in that:
 - the lipophilic active principle(s) have a log P greater than 2,
 - the surfactant(s) represent at least 50% by weight of the total weight of said composition,
 - the cosurfactant(s) are chosen from the good solvents for said active principle(s),
 - the lipophilic phase is optionally surface-active and represents less than 0.5 to 4.5% by weight of the total weight of said composition and has an HLB of less than or equal to 6, and
- when the active principle is different from a retinoid, then said composition additionally comprises a non-surfactant oily phase representing from 1 to 12% of the total weight of said composition.

2. The composition as claimed in claim 1, characterized in that the active principle(s) have a log P greater than 4.

3. The composition as claimed in claim 1 or 2, characterized in that the active principle(s) are chosen from retinoids, hypolipidemic agents, steroid hormones, steroid anti-inflammatories, nonsteroid anti-inflammatories (NSAIDs), antiretrovirals, protease inhibitors ("navirs"), antiacids, proton pump inhibitors, antiemetics, fat-soluble vitamins, cardiovascular system drugs, platelet aggregation inhibitors, cancer drugs, certain plant extracts and their isolated or

derived APs, immunosuppressants, central nervous system drugs, antimigraines, antibiotics, antifungals and antiparasitics.

4. The composition as claimed in claim 3, characterized in that the active principle(s) are chosen from retinoids, hypolipidemic agents and steroid hormones.

5. The composition as claimed in claim 3 or 4, characterized in that it contains isotretinoin in a quantity of between 1 and 2.5% by weight relative to the total weight of the composition.

6. The composition as claimed in claim 3 or 4, characterized in that it contains fenofibrate in a quantity of between 5 and 10% by weight relative to the total weight of the composition.

7. The composition as claimed in claim 2 or 3, characterized in that it contains progesterone in a quantity of between 3 and 7% by weight relative to the total weight of the composition.

8. The composition as claimed in any one of the preceding claims, characterized in that the surfactant(s) are chosen from polyglycolized C₈-C₁₈ glycerides, polysorbates or polyethylene glycols (PEG)-esters of C₁₂-C₁₈ fatty acids, macrogol and propylene glycol esters of C₈-C₁₈ fatty acids, macrogol-glyceride esters of C₁₂-C₁₈ fatty acids, polyglyceric esters of C₁₂-C₁₈ fatty acids, and mixtures thereof.

9. The composition as claimed in any one of the preceding claims, characterized in that the surfactant(s) represent from 70 to 85% of the total weight of the composition.

10. The composition as claimed in any one of the preceding claims, characterized in that the cosurfactant(s) are chosen from diethylene glycol monoethyl ether; N-methyl-2-pyrrolidone; the triester of glycerol and acetic acid; dimethyl isosorbate; polyethylene glycols; alcohols and glycols; mono- and diesters of propylene glycol and of caprylic, capric, lauric fatty acids; mono- and diglycerides of caprylic, capric, lauric, oleic, stearic fatty acids; and mixtures thereof.

11. The composition as claimed in any one of the preceding claims, characterized in that the cosurfactant(s) represent from 5% to 20% of the total weight of the composition.

12. The composition as claimed in claim 5, characterized in that the cosurfactant concentration is between 10 and 15% of the total weight of the composition.

13. The composition as claimed in claim 6, characterized in that the CoS concentration is between 5 and 10% of the total weight of the composition.

14. The composition as claimed in any one of the preceding claims, characterized in that the lipophilic phase has an HLB of less than or equal to 4, and is chosen from fatty acid esters; sorbitan esters of saturated or unsaturated fatty acids and their derivatives; glycerol, propylene or butylene glycol esters of fatty acids; medium chain triglycerides of caprylic, capric or lauric fatty acids; and mixtures thereof.

15. The composition as claimed in claim 14, characterized in that the fatty acid esters are chosen from macrogol (or polyethylene glycol) glycerides, in other words polyglycolized glycerides of fatty acids.

16. The composition as claimed in claim 5, characterized in that it contains a lipophilic phase in a proportion of between 3 and 4.5% by weight relative to the total weight of the composition.

17. The composition as claimed in claim 5, characterized in that it contains a nonsurfactant oily phase representing from 1 to 12% of the total weight of said composition and at least one thickening agent.

18. The composition as claimed in any one of the preceding claims, characterized in that the oily phase is chosen from oils of natural and synthetic origin.

19. The composition as claimed in claim 18, characterized in that the natural oils are chosen from almond, peanut, rapeseed, cotton seed, linseed, corn, olive, borage, evening primrose, fish, palm, palm kernel, grapeseed, sesame, soybean and sunflower oils.

20. The composition as claimed in claim 18, characterized in that the synthetic oils are chosen from fatty acid esters whose HLB value is between 1 and 3.

21. The composition as claimed in claim 6, characterized in that it contains an oily phase in a proportion of between 2 and 15% by weight.

22. The composition as claimed in any one of the preceding claims, characterized in that it leads, in the presence of a hydrophilic phase, to the formation of a microemulsion in which the size of the micelles is less than 500 nm, and more particularly between 1 and 200 nm.

23. The composition as claimed in any one of the preceding claims, characterized in that it is packaged in hard gelatin capsules or in soft gelatin capsules.

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[0127] The good results of permeability of the composition F3 containing isotretinoin alone is explained by the fact that this active principle was completely dissolved in DMSO; however, this excellent solvent for organic substances cannot be used as it is in pharmaceutical preparations for toxicity considerations.

EXAMPLE 3

Comparative Study of the Bioavailability of Isotretinoin as a Function of its Formulation

[0128] In order to carry out this study, the following pharmaceutical composition F4 in accordance with the invention was prepared:

Active principle: isotretinoin	2%
S: Labrasol® (HLB = 14)	80.5%
Co-S: Transcutol®	13.5%
Lipophilic phase: Labrafil® M1944 (HLB = 3)	4%

[0129] This pharmaceutical composition F4 was packaged in hard gelatin capsules each containing 9 mg of isotretinoin.

[0130] The bioavailability study was carried out according to a protocol for administering a single dose of each of the treatments: the test formula and the reference formula are administered according to a criss-cross and randomized order.

[0131] The isotretinoin formulated according to the pharmaceutical composition F4 was compared with that of the commercial formulation of isotretinoin sold under the trademark ROACCUTANE® and as described above in Example 2.

[0132] In order to observe the customary mode of administration and dosage of the reference proprietary product ROACCUTANE®, the two products were administered, during meals, at the rate of the single dose of 3 soft gelatin capsules of the composition F4 and two soft gelatin capsules of ROACCUTANE® at 20 mg.

[0133] The results obtained are presented in FIG. 1 which correspond to the plasma concentration of isotretinoin in ng/ml as a function of the time in hour.

[0134] At equal doses of AP isotretinoin, these results show a suprabioavailability of 37.5% for the composition F4, in terms of intensity of absorption, according to the comparative results of the areas under the total plasma concentration curves (AUC) and the plasma concentration peaks C_{max} (result greater than 48%, with in particular a lower variability of the pharmacokinetic response in the case of the composition F4).

[0135] These results also demonstrate a bioequivalence between the administered dose of 27 mg of isotretinoin (composition F4 in accordance with the invention) and the dose which is nevertheless greater than 40 mg of isotretinoin of ROACCUTANE®.

[0136] In terms of rate of absorption, these results also show that the composition F4 in accordance with the invention is more rapid than the reference composition ROACCUTANE®, with an earlier plasma concentration peak,

expressed by the parameter T_{max} , which is one hour on average for the composition F4, against 3 hours on average for ROACCUTANE®.

EXAMPLE 4

Pharmaceutical Composition Based on Fenofibrate

[0137] The following pharmaceutical composition F5, in accordance with the invention, was prepared:

Active principle: fenofibrate	8.1%
S: Labrasol® (HLB = 14)	74.0%
Co-S: Transcutol®	6.25%
Lipophilic phase: Labrafil® M1944	0.8%
Oily phase: Labrafac® PG (HLB = 1)	6.25%
Oily phase: Labrafac® CC (HLB = 1)	4.6%

[0138] In the presence of an aqueous phase, this composition spontaneously led to a stable and fine microemulsion in which the fenofibrate was perfectly dissolved.

EXAMPLE 5

Comparative Study of the Bioavailability of Fenofibrate as a Function of its Formulation

[0139] This study was carried out under the same conditions as those described above in Example 3, in order to compare the bioavailability of the fenofibrate formulated in accordance with the invention (composition F5 as described above in Example 4) to the commercial fenofibrate formulation (micronized form) sold under the trademark LIPANTHYL® 67M.

[0140] The composition F5 was packaged in hard gelatin capsules each containing 66 mg of fenofibrate.

[0141] The composition F5 and LIPANTHYL® was administered during a meal at the rate of 1 hard gelatin capsule.

[0142] The results obtained are presented in FIG. 2, which correspond to the plasma concentration of fenofibric acid in ng/ml as a function of the time in hour.

[0143] In terms of rate of absorption, the composition F5 is more rapid than LIPANTHYL®, with an earlier plasma concentration peak, expressed by the parameter T_{max} , which is 2.5 hours on average for the composition F5 against 5.83 hours on average for LIPANTHYL®.

[0144] This bioequivalence between the composition F5 and the dose of 67 mg of the formulation LIPANTHYL® is particularly advantageous insofar as the composition F5 is found to be bioequivalent to the formulation LIPANTHYL®, which is itself suprabioavailable compared to the previously marketed nonmicronized form.

[0145] Consequently, the self-emulsifying and micelle-forming composition F5 in accordance with the invention makes it possible to obtain the maximum bioavailability of the fenofibrate while applying to this active principle a galenic route of preparation which is completely different from micronization, whereas, up until now, only the micronization of fenofibrate had made it possible to improve its bioavailability.

EXAMPLE 6

Pharmaceutical Composition Based on Progesterone

[0146] The following pharmaceutical composition F6 in accordance with the invention was prepared:

Active principle: Progesterone	5%
S: Labrasol® (HLB = 14)	8.5%
S: Gelucire® 44/14 (HLB = 14)	65%
Co-S: Capryol® PGMC (HLB = 5 to 6)	17.5%
Lipophilic phase: Labrafil® M1944	2%
Oily phase: Labrafac® CC (HLB = 1)	2%

[0147] This composition is essentially distinguishable from the prior art composition F2, which is not stable after a few months, by the fact that it contains 4% of oily phase. It spontaneously leads, in the presence of an aqueous phase, to a stable and fine microemulsion in which the progesterone is perfectly dissolved.

[0148] Indeed, it should be noted that the lipophilicity of the AP plays an important role in the equilibrium of the system. The addition of the oily phase makes it possible to better solubilize the progesterone and it is this oil which will be micellized and which makes it possible to significantly improve the stability.

1. A self-micro emulsifying pharmaceutical composition for oral use comprising:

- at least one lipophilic active principle,
- at least one surfactant having a hydrophilic/lipophilic balance of less than 16,
- at least one cosurfactant,
- at least one lipophilic phase, characterized in that:
 - the lipophilic active principle(s) have a log P greater than 2,
 - the surfactant(s) represent at least 50% by weight of the total weight of said composition,
 - the cosurfactant(s) are chosen from the good solvents for said active principle(s),
 - the lipophilic phase is optionally surface-active and represents less than 0.5 to 4.5% by weight of the total weight of said composition and has an HLB of less than or equal to 6, and
 - when the active principle is different from a retinoid, then said composition additionally comprises a non-surfactant oily phase representing from 1 to 12% of the total weight of said composition.

2. The composition as claimed in claim 1, characterized in that the active principle(s) have a log P greater than 4.

3. The composition as claimed in claim 1 or 2, characterized in that the active principle(s) are chosen from retinoids, hypolipidemic agents, steroid hormones, steroid anti-inflammatories, nonsteroid anti-inflammatories (NSAIDs), antiretrovirals, protease inhibitors ("navirs"), antacids, proton pump inhibitors, antiemetics, fat-soluble vitamins, cardiovascular system drugs, platelet aggregation inhibitors, cancer drugs, certain plant extracts and their isolated or

derived APs, immunosuppressants, central nervous system drugs, antimigraines, antibiotics, antifungals and antiparasitics.

4. The composition as claimed in claim 3, characterized in that the active principle(s) are chosen from retinoids, hypolipidemic agents and steroid hormones.

5. The composition as claimed in claim 3 or 4, characterized in that it contains isotretinoin in a quantity of between 1 and 2.5% by weight relative to the total weight of the composition.

6. The composition as claimed in claim 3 or 4, characterized in that it contains fenofibrate in a quantity of between 5 and 10% by weight relative to the total weight of the composition.

7. The composition as claimed in claim 2 or 3, characterized in that it contains progesterone in a quantity of between 3 and 7% by weight relative to the total weight of the composition.

8. The composition as claimed in any one of the preceding claims, characterized in that the surfactant(s) are chosen from polyglycolized C₈-C₁₈ glycerides, polysorbates or polyethylene glycols (PEG)-esters of C₁₂-C₁₈ fatty acids, macrogol and propylene glycol esters of C₈-C₁₈ fatty acids, macrogol-glyceride esters of C₁₂-C₁₈ fatty acids, polyglyceric esters of C₁₂-C₁₈ fatty acids, and mixtures thereof.

9. The composition as claimed in any one of the preceding claims, characterized in that the surfactant(s) represent from 70 to 85% of the total weight of the composition.

10. The composition as claimed in any one of the preceding claims, characterized in that the cosurfactant(s) are chosen from diethylene glycol monoethyl ether; N-methyl-2-pyrrolidone; the triester of glycerol and acetic acid; dimethyl isosorbate; polyethylene glycols; alcohols and glycols; mono- and diesters of propylene glycol and of caprylic, capric, lauric fatty acids; mono- and diglycerides of caprylic, capric, lauric, oleic, stearic fatty acids; and mixtures thereof.

11. The composition as claimed in any one of the preceding claims, characterized in that the cosurfactant(s) represent from 5% to 20% of the total weight of the composition.

12. The composition as claimed in claim 5, characterized in that the cosurfactant concentration is between 10 and 15% of the total weight of the composition.

13. The composition as claimed in claim 6, characterized in that the CoS concentration is between 5 and 10% of the total weight of the composition.

14. The composition as claimed in any one of the preceding claims, characterized in that the lipophilic phase has an HLB of less than or equal to 4, and is chosen from fatty acid esters; sorbitan esters of saturated or unsaturated fatty acids and their derivatives; glycerol, propylene or butylene glycol esters of fatty acids; medium chain triglycerides of caprylic, capric or lauric fatty acids; and mixtures thereof.

15. The composition as claimed in claim 14, characterized in that the fatty acid esters are chosen from macrogol (or polyethylene glycol) glycerides, in other words polyglycolized glycerides of fatty acids.

16. The composition as claimed in claim 5, characterized in that it contains a lipophilic phase in a proportion of between 3 and 4.5% by weight relative to the total weight of the composition.

17. The composition as claimed in claim 5, characterized in that it contains a nonsurfactant oily phase representing from 1 to 12% of the total weight of said composition and at least one thickening agent.

18. The composition as claimed in any one of the preceding claims, characterized in that the oily phase is chosen from oils of natural and synthetic origin.

19. The composition as claimed in claim 18, characterized in that the natural oils are chosen from almond, peanut, rapeseed, cotton seed, linseed, corn, olive, borage, evening primrose, fish, palm, palm kernel, grapeseed, sesame, soybean and sunflower oils.

20. The composition as claimed in claim 18, characterized in that the synthetic oils are chosen from fatty acid esters whose HLB value is between 1 and 3.

21. The composition as claimed in claim 6, characterized in that it contains an oily phase in a proportion of between 2 and 15% by weight.

22. The composition as claimed in any one of the preceding claims, characterized in that it leads, in the presence of a hydrophilic phase, to the formation of a microemulsion in which the size of the micelles is less than 500 nm, and more particularly between 1 and 200 nm.

23. The composition as claimed in any one of the preceding claims, characterized in that it is packaged in hard gelatin capsules or in soft gelatin capsules.

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