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Delegatura de propiedad Industrial

División de Nuevas Creaciones

PCT
SOLICITUD

SS.

PATENTE DE INVENCION

07-23970

21. EXPEDIENTE No.

54. TÍTULO Composiciones de Administración
prolongada de hormonas con base en
poliorganosiloxanos o etileno - acetato de Vinilo
resp. Proceso para su fabricación.

51. CLASIFICACIÓN INTERNACIONAL

71. SOLICITANTE Biolab Sanus Farmaceutica LTDA.

DOMICILIO Sao Paulo, Brasil.

74. APODERADO Laura Michelsen Niño.

22. BOGOTÁ, D. C., 09/03/07.

bl.



PETITORIO

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Ita 11 PATENTEEYII
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FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

① SOLICITUD DE :
☒ Patente de Invención. ☐ Patente de Modelo de Utilidad
☒ Capítulo I ☐ Capítulo II

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⑥ Título (54) Composiciones de administración prolongada de hormonas con base en
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⑦ Clasificación Internacional (51) _____

⑧ Prioridad SI ☒ NO ☐	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
	BRASIL	09/08/2004	PI 0406247-7
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⑨ Comprobante de pago No. _____ Fecha _____

Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

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ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud
- ☐ Documento que acredite la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☐ Poderes, si fuere el caso.
- ☐ Documento de cesión del inventor al solicitante o a su causante
- ☐ Declaraciones
- ☒ Copia de la solicitud internacional (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano (Resumen, descripción, reivindicaciones, dibujos)
- ☐ Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA)
- ☐ Traducción del examen preliminar internacional efectuado por la IPEA
- ☐ De ser el caso, copia del contrato de acceso
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- ☐ De ser el caso, certificado de depósito del material biológico
- ☐ Arte final 12x12.
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud
- ☐ De ser el caso, modificaciones efectuadas a la solicitud internacional
- ☒ Otros

11 FIGURA CARACTERÍSTICA:

12

Solicito la concesión de la patente,

NOMBRE LAURA MICHELSEN IÑO

FIRMA:

C.C. 39 783 287

T.P. 67 897

Instrucciones para la presentación de los anexos, ver reverso de esta página.

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FECHA : MARZO 9 DE 2007

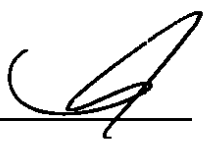
***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	Nº. PAGO	FECHA PGO	Vr. PAGO
TRIANA URIBE & MICHELSEN CONSIGNACION		BANCO POPULAR	050-00110-6	63060360	09/03/2007	6,052,030.00
TRIANA URIBE & MICHELSEN CONSIGNACION		BANCO POPULAR	050-00110-6	63068363	09/03/2007	110,000.00

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

CONCEPTO	TOTAL CONCEPTO
1. RENTISTICO	
1 50005-01-01 SOLICITUDES	
1 TRAMITES DE SOL. DE PATENTE DE IN	482,000.00
TOTAL :	\$ 482,000.00

SON: CUATROCIENTOS OCHENTA Y DOS MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

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A

**COMPOSICIONES DE ADMINISTRACIÓN PROLONGADA DE
HORMONAS CON BASE EN POLIORGANOSILOXANOS O
ETILENO - ACETATO DE VINILO RESP. PROCESO PARA SU
FABRICACIÓN.**

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MEMORIA DESCRIPTIVA

Campo de la Invención

La presente invención se relaciona con mejoras en composiciones de administración prolongada de hormonas dentro del cuerpo humano, más particularmente con una composición biocompatible, no biodegradable, que comprende una matriz de polímero reticulada por radiación ionizante donde hay una hormona dispersa. En otros aspectos se refiere al uso de esta composición para obtener un dispositivo de administración prolongada de hormonas, un proceso para fabricar este dispositivo, y a un método de tratamiento de condiciones o disfunciones del organismo humano.

Fundamentos de la Invención

Son conocidos los medios para la liberación controlada de drogas en el interior del cuerpo humano, en los cuales principios activos y preparaciones farmacéuticas son mezclados con vehículos farmacéuticamente apropiados son introducidos en el cuerpo de los pacientes. Ya en el organismo, el vehículo se desintegra o se biodegrada lentamente, permitiendo la liberación lenta de la droga. Sin embargo, los vehículos empleados en la actualidad no siempre corresponden a resultados biológicos y farmacéuticos satisfactorios. No es el caso de la presente invención.

Otro medio común para la obtención de liberación controlada y la encapsulación del principio activo con revestimientos biodegradables, por ejemplo, derivados de celulosa, amidos y polisacáridos, técnica que ha sido ampliamente usada para la liberación controlada de analgésicos. Sin embargo, esta droga encapsulada presenta problemas en su utilización, tal como dificultad para ser localizada dentro del cuerpo y retirada - por

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ejemplo en caso de reacción alérgica - además de una difícil obtención de distribución apropiada del espesor del revestimiento (de modo que proporcione la liberación deseada) y el tiempo de latencia del agente revestido en el tracto intestinal relativamente corto, tornando su uso poco eficiente para la liberación prolongada. No es el caso de la presente invención).

La patente norteamericana US 3.279.996 se refiere a un dispositivo para la liberación lenta de drogas, típicamente una matriz de goma de siliconas, o sea, un organopolisiloxano vulcanizado en caliente o en temperatura ambiente (llamado RTV, "room temperature vulcanizing" (vulcanización a temperatura ambiente)) donde está dispersa la droga.

La patente norteamericana US 3.948.254 se refiere a un vehículo que contiene una droga y a un envoltorio para este vehículo, ambos permeables al pasaje de la droga a ser dispensada. La velocidad del pasaje de la droga por el envoltorio es menor que la velocidad de pasaje de la droga a través del vehículo sólido, por difusión. El vehículo es típicamente un poliorganosiloxano, obtenido por procesos tradicionales.

La patente norteamericana US 4.957.119 se refiere a un implante de material polimérico para la administración lenta de un agente contraceptivo. El material polimérico está compuesto por un núcleo y por una capa externa, ambos de copolímero de etileno/acetato de vinilo, separados por una membrana. El dispositivo es obtenido por co-extrusión, por lo tanto a alta temperatura.

La patente norteamericana US 6.117.442 se refiere a un dispositivo de administración de velocidad controlada para un agente terapéuticamente activo, que comprende un núcleo de

siloxano fluorado (grupos 3,3,3-trifluoropropilo ligados a los átomos de silicio del grupo siloxano), y una membrana envolvente elastomérica. El dispositivo es obtenido por procesos tradicionales.

En la técnica previa se ha verificado que, independientemente de la manera cómo se dispone el material que sirve de matriz para la liberación de la droga en él dispersa, su polimerización, o reticulación, siempre se realiza en caliente o catalíticamente en presencia de solventes. En cualquiera de estas alternativas hay perjuicios en el desempeño del administrador de la droga, o sea:

- cuando hay calor involucrado en la reticulación, hay mayor degradación, tanto del polímero como del principio activo disperso en el polímero,

- cuando la reticulación es catalítica, hay mayor contaminación por solventes y catalizadores eventualmente retenidos en el polímero, lo cual exige etapas posteriores de purificación.

En consecuencia,, los polímeros reticulables por sistemas catalíticos, en presencia de solventes, o en altas temperaturas, sufren el perjuicio de sus propiedades mecánicas y químicas, generando adicionalmente oligómeros que perjudican su uso para aplicación subcutánea.

La presente invención se relaciona con una matriz polimérica y un dispositivo menos propensos a los problemas del estado de la técnica, de manera simple y con una ventajosa relación costo-beneficio. Esto se debe al empleo de radiación ionizante para obtener la reticulación del polímero que sirve de matriz para la liberación controlada de la hormona a ser dispensada,

independientemente de las altas temperaturas, presencia de catalizadores o solventes. La cura o reticulación de materiales poliméricos en frío por medio del uso de radiación ionizante es ventajosa pues no depende de la presencia de catalizadores o aditivos y puede ser realizada a cualquier temperatura. La ausencia de catalizadores e iniciadores químicos garantiza la obtención de productos muchos más puros que evitan costosas etapas de purificación, además de evitar el riesgo de sobrecalentamiento localizado que provoca la fuerte degradación del polímero, o que podría generar subproductos tóxicos (A. Bhattacharya, Radiation and Industrial Polymers (Radiación y Polímeros Industriales), Prog. Polym Sci. 25 (2000) pp. 371-401). Además de esto, las hormonas no son sometidas a temperaturas de desactivación o descomposición preservando, por lo tanto, su potencial de acción y evitando la formación de subproductos tóxicos.

El régimen de dosificación de las hormonas contenidas en los dispositivos de acuerdo con la presente invención varía de acuerdo con factores conocidos, tales como las características farmacodinámicas del agente específico; la especie, edad, sexo, salud, condiciones médicas y peso del paciente; la naturaleza y duración de los síntomas; el tipo de tratamiento concurrente y el efecto deseado. Un médico podrá determinar y prescribir la cantidad y la velocidad eficaz de liberación de la hormona a ser administrada al paciente.

La radiación ionizante utilizada en la invención, típicamente radiación gama, o de haz de electrones, penetra totalmente en el cuerpo de la matriz polimérica, reaccionando solo con los electrones, sin precipitar la formación de isótopos.

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Debe tenerse en cuenta que el empleo de otros tipos de radiación, como UV, propician polimerización sustancialmente superficial, y no están contemplados por la invención. El polímero base de la matriz polimérica es más puro, evitando etapas costosas de purificación.

Así, la presente invención se refiere a una composición de administración prolongada de hormonas, caracterizada por comprender una matriz de polímero biocompatible no biodegradable, reticulada por radiación ionizante, teniendo dicha matriz una o más hormonas dispersas en ella.

En otro aspecto la invención contempla el uso de una composición de este tipo caracterizado por ser utilizado en la fabricación de un dispositivo para la administración controlada de hormonas en el cuerpo humano.

La presente invención trata también con un método de tratamiento de condiciones o disfunciones, caracterizado por la inserción y mantenimiento de dicha composición dentro del cuerpo humano durante el tiempo suficiente para que dicha hormona sea administrada al cuerpo de forma prolongada.

Descripción de las Figuras.

Figura 1: Muestra el esquema de la recolección de muestras de sangre del mamífero.

Figura 2: Muestra resultados de las muestras correspondientes a las medias de liberación de 17- β -estradiol durante el período de ensayo

Descripción de la Invención

Una primera finalidad de la presente invención es una composición de administración prolongada de hormonas, caracterizada por tener (1) una matriz polimérica biocompatible,

no biodegradable, reticulada por medio de radiación ionizante, y (2) una hormona dispersa en dicha matriz polimérica. Esta composición hace uso del fenómeno de la difusión en la cual un principio activo migra a través de la matriz polimérica con una velocidad prolongada y/o controlada.

La matriz polimérica de acuerdo con la presente invención puede comprender cualquier polímero biocompatible, no sustancialmente biodegradable, de origen natural o sintético. Como saben los expertos en la técnica, en forma general los polímeros de alta masa molecular son biocompatibles debido a su inercia química. Dicha matriz propicia propiedades químicas y mecánicas importantes y permite la difusión optimizada del principio activo contenido dentro de la misma hacia el lugar de absorción dentro del cuerpo del usuario. Pueden citarse como polímeros biocompatibles los poliorganosiloxanos de forma general, particularmente los polidialquilsiloxanos como los polidimetilsiloxanos, y el EVA (copolímero de etileno y acetato de vinilo), sin exclusión de cualquier otro, que sean reticulables por radiación ionizante.

Las hormonas pasibles de ser utilizadas por la invención son aquellas aceptables farmacéuticamente y capaces de ser administradas de forma prolongada dispersas en la matriz polimérica. Pueden tener forma líquida o sólida, prefiriéndose esta última. Un ejemplo particular son los estrógenos, eficaces en el tratamiento de condiciones existentes en el cuerpo animal, particularmente el humano, o en los fluidos del cuerpo. La velocidad de liberación de la hormona dependerá de la afinidad de cada conjunto matriz-principio activo donde la velocidad de liberación de cada conjunto debe ser verificada, según lo saben

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los expertos en la técnica. La hormona puede ser llevado en la matriz hasta la concentración límite que permita su reticulación y la obtención de propiedades mecánicas adecuadas. Por lo tanto, estos límites dependen de cada matriz y de cada principio activo, determinados por los expertos en la técnica.

Particularmente, la hormona es un estrógeno, por ejemplo utilizado en la reposición hormonal, tratamiento de vaginitis, terapia del cáncer de próstata y algunos casos de cáncer de mama o como anticonceptivo. Particularmente se utiliza el beta-estradiol.

La composición de la invención también puede contener otros ingredientes, como cargas inertes presentes en la matriz polimérica, en valores de hasta cerca de 80% en peso.

La composición de la invención puede contener, también optativamente, un marcador radio-opaco, o sea, visible a los rayos X, para facilitar su localización, por ejemplo cuando se utiliza en un implante, en caso que se exija su localización debido a que hubiera ocurrido la migración accidental del lugar de colocación. El marcador puede ser cualquier compuesto conocido en la técnica, por ejemplo sulfato de bario. La cantidad de sulfato de bario está particularmente por encima de 0,1% en peso con relación al resto de la composición, suficiente para tonar el dispositivo visible a los rayos X, estando preferiblemente su contenido comprendido entre 0,1% y 2% en peso.

Una segunda finalidad de la presente invención es el uso de dicha composición en la fabricación de un dispositivo de administración prolongada de hormonas al cuerpo humano, por ejemplo por implante subcutáneo, o un inserto en el cuerpo humano que actúe como una glándula artificial.

Otra finalidad de la invención son dispositivos de administración prolongada de hormonas al cuerpo humano, caracterizados por comprender una composición que contiene una matriz polimérica como la descrita.

El dispositivo de administración de la invención puede estar también optativamente dotado de un envoltorio, para aumentar el control de la velocidad de liberación del principio activo. Este envoltorio puede ser del mismo material que la matriz polimérica, o de material diferente. Los expertos en la técnica sabrán dimensionar este envoltorio, basados en los datos disponibles en el estado de la técnica.

El dispositivo de administración de la invención puede tener geometrías variadas, tales como bandas de secciones transversales variadas, bastones, cilindros y tubos esféricos, preferiblemente tubos esféricos. Particularmente, tiene la forma de un bastón de 1 a 12 cm de largo, preferiblemente de 2 a 4 cm y de aproximadamente 0,3 a 10 mm de diámetro, preferiblemente 2 a 4 mm.

Otra finalidad de la presente invención es un proceso de producción del dispositivo para la administración prolongada de hormonas en el cuerpo humano. Dicho proceso comprende las etapas de:

- (i) Mezclar uno o más polímeros biocompatibles, no sustancialmente biodegradables con una o más hormonas, y aditivos si los hubiera;
- (ii) Moldear en frío dicha mezcla, en la forma deseada;
- (iii) Desmoldar en frío;
- (iv) envasar el producto obtenido

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(v) exponer el producto envasado a radiación ionizante suficiente para reticular el polímero y esterilizar el producto envasado.

Se utiliza particularmente radiación gama o haz de electrones.

Una de las ventajas de irradiar el producto ya envasado es el hecho de que se obtienen concomitantemente la reticulación del material polimérico que compone la matriz polimérica, y la esterilización del dispositivo de la invención ya envasado.

Dentro de las alternativas de realización, hay etapas optativas que pueden formar parte del proceso de la invención, por ejemplo:

- exponer la mezcla moldeada de la etapa (ii) mencionada a radiación ionizante, para pre-reticularla y ya iniciar la esterilización;

- después del desmolde de la etapa (iii), revestir el material con un envoltorio, particularmente de material polimérico biocompatible, optativamente con el mismo material polimérico del punto (i).

De forma particular, el polímero del punto (i) y el envoltorio optativo son de poliorganosiloxano, más particularmente polidimetilsiloxano.

También otra finalidad de la presente invención es un método de tratamiento de condiciones o disfunciones del cuerpo humano, caracterizado porque utiliza el dispositivo obtenido según el proceso descrito más arriba, particularmente como implante subcutáneo. El dispositivo de la invención también puede utilizarse en el tratamiento de condiciones o disfunciones en forma de un inserto anal, vaginal, oral, nasal, o cualquier otro.

A continuación se presenta un ejemplo de utilización del dispositivo de la invención, sin que esto implique limitación alguna aparte de las contenidas en las reivindicaciones anexas.

Ejemplo

Ensayo In Vivo

Se preparan implantes, de forma cilíndrica, con un diámetro de 2 mm y 20 mm de largo constituidos por polidimetilsiloxano, 50 mg de 17β -estradiol y sulfato de bario como radio-marcador. Para inyectar los implantes, se utilizaron jeringas descartables heparinizadas Crestar® dado que la sangre debe ser obtenida por la punción venosa con una aguja de 25x8.

Se inyectó en un mamífero, por vía subcutánea, un implante en la región dorsal superior, entre las paletas para facilitar la aplicación, esta región fue depilada.

Se recolectan muestras de sangre del mamífero algunos días antes de la colocación del implante y por un período de aproximadamente 17 días después de la colocación del mismo. Después de este período se recogieron 10 muestras más con un intervalo semanal, como se ve en la Figura 1. La muestra recolectada antes de la colocación del implante sirve para confirmar la inexistencia de estradiol circulante.

Las muestras recolectadas fueron centrifugadas a 1000 revoluciones durante 5 minutos. Se separó el sobrenadante (plasma) y se guardó a -20°C en tubos Eppendorf hasta la realización de los ensayos. Luego, se graficaron los resultados de las muestras correspondientes a las medias de liberación de 17β -estradiol durante el período de ensayo, como se ve en la Figura 2.

REIVINDICACIONES

1. Composición para la administración prolongada de hormonas, CARACTERIZADA por comprender una matriz de polímero biocompatible, no biodegradable, reticulada por radiación ionizante, teniendo dicha matriz una o más hormonas dispersas en ella.

2. Una composición, de acuerdo con la reivindicación 1, CARACTERIZADA porque dicho polímero biocompatible es seleccionado entre los poliorganosiloxanos, particularmente los polidialquilsiloxanos como los polidimetilsiloxanos, y el etileno-acetato de vinilo.

3. Una composición, de acuerdo con la reivindicación 1, CARACTERIZADA porque dicha hormona es farmacéuticamente aceptable, capaz de ser administrada por difusión de forma prolongada dispersa en dicha matriz polimérica.

4. Una composición, de acuerdo con la reivindicación 1, CARACTERIZADA porque dicha hormona es seleccionada entre los estrógenos.

5. Una composición, de acuerdo con la reivindicación 1, CARACTERIZADA porque dicha hormona es un estrógeno, particularmente el beta-estradiol.

6. Una composición, de acuerdo con la reivindicación 1, CARACTERIZADA porque contiene hasta aproximadamente 80% en peso de cargas inertes.

7. Una composición, de acuerdo con la reivindicación 1, CARACTERIZADA porque contiene un marcador radio-opaco, particularmente más de 0,1% en peso, más particularmente entre 0,1% y 2%.

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8. Uso de una composición de acuerdo con cualquiera de las reivindicaciones 1 a 7, CARACTERIZADO por estar involucrado en la fabricación de un dispositivo de administración prolongada de hormonas al cuerpo humano.

9. Uso, de acuerdo con la reivindicación 8, CARACTERIZADO porque dicho dispositivo es un implante subcutáneo.

10. Dispositivo de administración prolongada de hormonas al cuerpo humano, CARACTERIZADO por comprender una composición de acuerdo con una de las reivindicaciones 1 a 7.

11. Un dispositivo de acuerdo con la reivindicación 10, CARACTERIZADO porque tiene un envoltorio, del mismo material de dicha matriz polimérica, o de un material diferente.

12. Un dispositivo de acuerdo con la reivindicación 10, CARACTERIZADO porque dicho dispositivo tiene una geometría seleccionada entre bandas, bastones, cilindros o tubos.

13. Un dispositivo de acuerdo con la reivindicación 12, CARACTERIZADO porque dicho dispositivo tiene la forma de un tubo.

14. Un dispositivo, de acuerdo con la reivindicación 12, CARACTERIZADO porque dicho dispositivo tiene la forma de un bastón de aproximadamente 1 cm a aproximadamente 12 cm de largo, y de aproximadamente 0,3 mm a aproximadamente 10 mm de diámetro.

15. Un dispositivo, de acuerdo con la reivindicación 14, CARACTERIZADO porque dicho dispositivo tiene la forma de un bastón de aproximadamente 1 cm a aproximadamente 4 cm de largo, y de aproximadamente 2 mm a aproximadamente 4 mm de diámetro.

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16. Un proceso para la producción de un dispositivo para la administración prolongada de hormonas al cuerpo humano, de acuerdo con una de las reivindicaciones 10 a 15, CARACTERIZADO por comprender las etapas de (i) mezclar uno o más polímeros biocompatibles, no sustancialmente biodegradables con una o más hormonas, y aditivos, si los hubiera; (ii) moldear en frío dicha mezcla, en la forma deseada; (iii) desmoldar en frío; (iv) envasar el producto obtenido; (v) exponer el producto envasado a radiación ionizante suficiente para reticular el polímero y esterilizar el producto embalado.

17. Un proceso de acuerdo con la reivindicación 16, CARACTERIZADO porque dicha radiación ionizante es seleccionada entre radiación gama y haz de electrones.

18. Un proceso de acuerdo con la reivindicación 16, CARACTERIZADO porque, después de la etapa (ii) de moldeo de la mezcla en frío, se expone la mezcla a radiación ionizante.

19. Un proceso de acuerdo con la reivindicación 16, CARACTERIZADO porque, después de la etapa (iii) de desmolde en frío, se reviste el material con un envoltorio, particularmente de material polimérico biocompatible, optativamente el mismo material polimérico de (i).

20. Método para el tratamiento de condiciones o disfunciones del cuerpo humano, CARACTERIZADO por ser efectuado por la inserción y mantenimiento de la composición según una de las reivindicaciones 1 a 8 en el interior del cuerpo humano durante un tiempo suficiente para que dicha hormona sea administrada de forma adecuada al cuerpo.

21. Un método para el tratamiento de condiciones o disfunciones del cuerpo humano, CARACTERIZADO por la inserción

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y mantenimiento del dispositivo de acuerdo con una de las reivindicaciones 10 a 15, en el interior del cuerpo humano durante un tiempo suficiente para que dicha hormona sea administrada en forma adecuada al cuerpo.

pp. BIOLAB SANUS FARMACEUTICA LTDA

P-7183-Q

Santiago, Chile, Febrero de 2006.

18 19

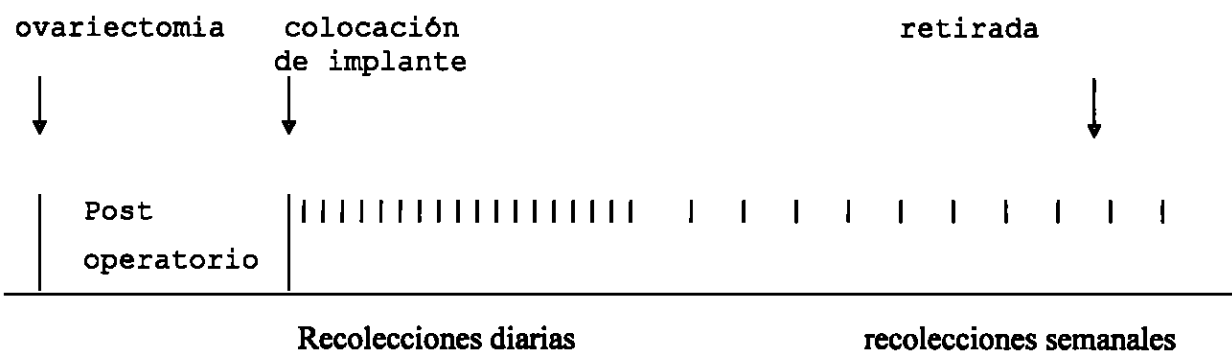


FIGURA 1

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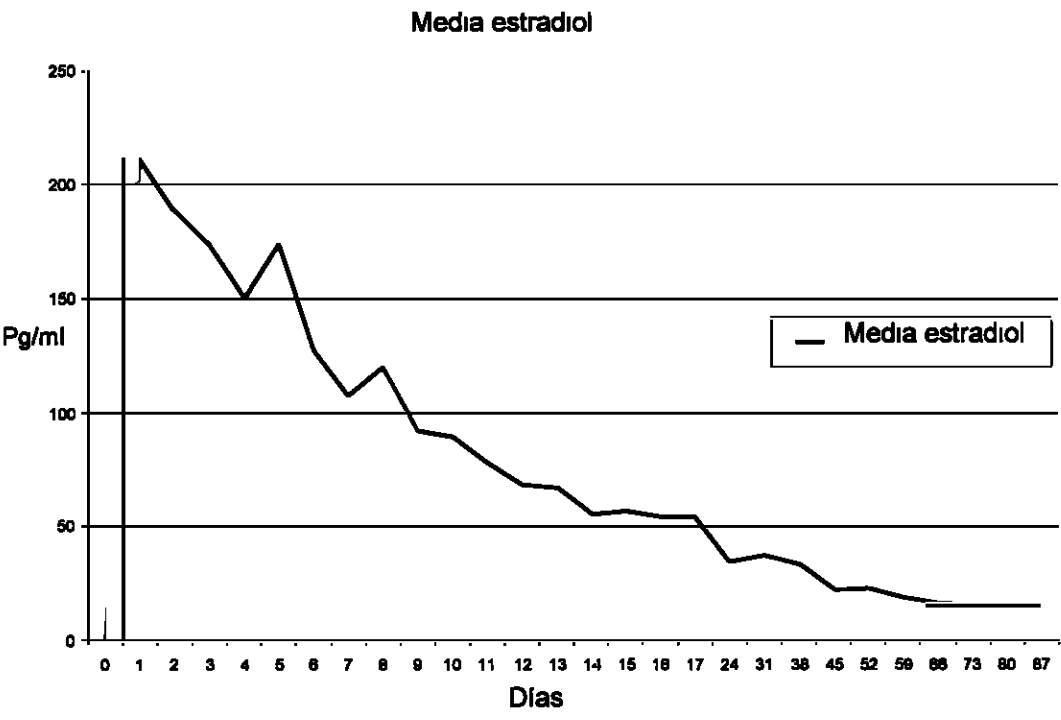


FIGURA 2

" Hormone delayed release composition on the basis of polyorganosiloxanes or ethylene vinyl acetate resp. process for its manufacture. "

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FIELD OF THE INVENTION

The present invention refers to an improvement in hormone delayed release compositions within the human body, more particularly to a non-biodegradable biocompatible composition comprising a polymeric matrix crosslinked by ionizing radiation wherein a hormone is dispersed. In other aspects,
10 the present invention refers to the use of said composition to obtain a hormone delayed release device, to the process for the manufacture of said device, and to a method for the treatment of conditions or dysfunctions of the human body.

BACKGROUND THE INVENTION

Means for the controlled release of drugs within the human body
15 are known, in which active principles and pharmaceutical preparations are mixed with pharmaceutically appropriate vehicles and inserted in the patient bodies. While in the organism, the vehicle disintegrates or slowly biodegrades, allowing slow drug release. However, currently used vehicles not always correspond to satisfactory biological and pharmaceutical results. This is not the
20 case of the present invention.

Another common mean to obtain delayed release is to encapsulate the active principle with biodegradable coatings, such as cellulose derivatives, starches and polysaccharides, a technical widely used for the analgesics controlled release. However, said encapsulated drug presents
25 problems for its use, such as difficulty to be located within the body and removed - for example, in case of allergic reactions - besides the difficulty of obtaining an appropriate distribution of the coating thickness (in order to provide the desired release) and the latency period of the coated agent in the

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gastrointestinal treat is relatively short, causing low efficacy of its use for delayed release. This is not the case of the present invention.

US 3,279,996 refers to a slow drug release device, typically a silicon rubber matrix, i.e., a high or room temperature vulcanized organopolysiloxane (called RTV, "Room Temperature Vulcanizing"), wherein
5 the drug is dispersed.

US 3,948,254 refers to a vehicle containing a drug and an outside layer for said vehicle, both permeable to the passage of the drug to be released. The rate of passage of the drug through the outside layer is lower than the rate
10 of passage of the drug through the solid vehicle, by diffusion. The vehicle is typically a polyorganosiloxane, obtained by traditional processes.

US 4,957,119 refers to an implant of polymeric material for slow releasing of a contraceptive agent. The polymeric material is made of a core and an outside layer, both made of ethylene/vinyl acetate copolymer, separated
15 by a membrane. The device is obtained by coextrusion, and therefore, under high temperature.

US 6,117,442 refers to a controlled rate release device for a therapeutically active agent, comprising a core of fluorinated siloxane (3,3,3-trifluoropropyl groups linked to the silicon atoms of the siloxane group) and an
20 elastomeric covering membrane. The device is obtained by traditional processes.

It can be verified in the prior art that, no matter the way on how the material acting as a matrix is placed to release the drug dispersed therein, its polymerization or crosslinking is always carried out hot or catalytically in the
25 presence of solvents. In any of these alternatives, there is loss to the performance of the drug dispenser, i.e.:

- when heat is involved in crosslinking, there is a higher degradation of the polymer or of the active principle dispersed therein;

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- in case of catalytic crosslinking, there is a higher contamination by solvents and catalysts eventually retained in the polymer, thus requiring later purification stages.

Therefore, catalytic systems crosslinkable polymers in the presence of solvents or under high temperatures, suffer loss of their mechanic and chemical properties, additionally generating oligomers which damage their use for subcutaneous application.

The present invention provides a polymeric matrix and a device which are less susceptible to the problems of the prior art, in a simple way and with an advantageous cost-benefit ratio. This is due to the use of ionizing radiation to crosslink the polymer acting as a matrix for the hormone controlled release to be released, not depending on high temperatures, or the presence of catalysts or solvents. The cold cure or crosslinking of polymeric materials by means of the use of ionizing radiation is advantageous since it does not depend on the presence of catalysts or additives and may be made under any temperature. The lack of catalysts and chemical initiators assures to obtain much purer products not requiring expensive purification stages, besides avoiding the risk of local overheating causing strong polymer degradation, which could generate toxic byproducts (A. Bhattacharya, *Radiation and Industrial Polymers*, Prog. Polym. Sci. 25 (2000) pages 371-401). Furthermore, hormones are not submitted to inactivation or decomposition temperatures, thus preserving their potential of action and avoiding the formation of toxic byproducts.

The dosage regimen for the hormones contained in the devices of the present invention varies according to known factors, such as the pharmacodynamic characteristics of the particular agent; the species, age, sex, health, medical conditions, and weight of the patient; the nature and extent of the symptoms; the sort of concurrent treatment; and the desired effect. A

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physician knows how to determine and prescribe the quantity and efficient rate of releasing of the hormone to be administered to the patient.

Ionizing radiation as used in the invention, typically gamma radiation or beam of electrons, fully penetrates in the body of the polymeric matrix, just reacting with electrons, not providing the formation of isotopes. It can be verified that the use of other types of radiation, like UV, provide substantially surface polymerization and are not an object of the present invention. The base polymer of the polymeric matrix is purer, not requiring expensive purification stages.

The present invention therefore refers to a hormone delayed release composition, characterized in that it comprises a non-biodegradable biocompatible polymer matrix, crosslinked by ionizing radiation, wherein said matrix comprises one or more hormones dispersed therein.

In another aspect, the invention refers to the use of said composition characterized in that it is for the manufacture of a device for hormones controlled release within the human body.

The present invention also refers to a method for the treatment of conditions or dysfunctions, characterized in that it is by inserting and maintaining said composition inside the human body for enough time for said hormone to be delayed released within the body.

DESCRIPTION OF THE INVENTION

A first object of the present invention is a hormone delayed release composition characterized in that it comprises (1) a non-biodegradable biocompatible polymeric matrix, crosslinked by means of ionizing radiation, and (2) a hormone dispersed in said polymeric matrix. This composition makes use of the diffusion phenomenon, according to which an active principle migrates through the polymeric matrix under delayed and/or controlled rate.

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The polymeric matrix of the present invention may comprise any substantially non-biodegradable biocompatible polymer of natural or synthetic origin. As known by a person skilled in the art, polymers with high molecular mass are generally biocompatible due to their chemical inertia. Said matrix
5 provides important chemical and mechanical properties and allows optimized diffusion of the active principle contained therein to the site of absorption inside the user body. As biocompatible polymers, polyorganosiloxanes in general, particularly polydialkylsiloxanes, such as polydimethylsiloxanes and EVA (ethylene and vinyl acetate copolymer) can be recited, with no exclusion of any
10 other, provided it is crosslinkable by ionizing radiation.

The hormones which may be used by the invention are pharmaceutically acceptable ones, which may be delayed released, being dispersed within the polymeric matrix. They may be available under liquid or solid form, and the latter one is preferred. A particular example, are estrogens,
15 efficient for the treatment of existing conditions in the animal body, particularly humans, or in the body fluids. The hormone releasing rate will depend on the affinity of each matrix-active principle set, wherein the release rate of each set should be verified, as the known by a person skilled in the art. The hormone may be loaded to the matrix until a limit concentration allowing its crosslinking
20 and until the obtainment of appropriated mechanical properties. These limits, therefore, depend on each matrix and each active principle, as determined by a person skilled in the art.

Particularly, the hormone is an estrogen used, for example, for hormone reposition, vaginitis treatment, prostate cancer therapy and some
25 cases of breast cancer, or as a contraceptive. β -estradiol is particularly used.

The composition of the present invention may also comprise other ingredients, such as inert fillers present in the polymeric matrix, under values of up to about 80% by weight.

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The composition of the present invention may also optionally comprise a radio-opaque marker, i.e. visible to X-ray, in order to facilitate its location, e.g. when used in implant, in case its location is required after accidental migration from the site of placement. The marker may be any
5 compound known in the art, e.g. barium sulfate. The amount of barium sulfate is particularly of more than 0.1% by weight in relation to the rest of the composition, which is enough to make the device visible to X-ray, preferably between 0.1% and 2% by weight.

A second object of the present invention is the use of said
10 composition for the manufacture of a hormone delayed release device within the human body, e.g. by subcutaneous implantation, or an insert to the human body acting as an artificial gland.

Another object of the present invention is hormone delayed release devices within the human body, which comprise the composition
15 containing the polymeric matrix as disclosed.

The release device of the present invention may also optionally comprise an outside layer to improve the control of the active principle release rate. Such outside layer may be made of the same material as the polymeric matrix, or a different material. A person skilled in the art knows how to establish
20 the measurements of said outside layer, based on available data in the prior art.

The release device of the present invention may present various geometries, such as bands with various crosswise sections, sticks, cylinders and spherical tubes, preferably spherical tubes. It has particularly the shape of a 1-12 cm long stick, preferably 2 to 4 cm and about 0.3 to 10 mm diameter,
25 preferably 2 to 4 mm.

Another object of the present invention is a process for the manufacture of a device for hormone delayed release within the human body. Said process comprises the steps of:

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- (i) Mixing one or more substantially non-biodegradable biocompatible polymers with one or more hormones and additives, if any;
 - (ii) Cold molding said mixture into the desired shape;
 - (iii) Cold de-molding;
 - (iv) Packing the obtained product;
 - (v) Exposing the packed product to enough ionizing radiation to crosslink the polymer and sterilize the packed product.

Gamma radiation or beam of electrons is particularly used.

10 One of the advantages of irradiating the already packed product is the fact that the polymeric material composing the polymeric matrix is crosslinked simultaneously to the sterilization of the already packed device of the present invention.

15 Within embodiment alternatives, there are optional steps which may be a part of the process of the invention, such as:

- to expose the molded mixture of step (ii) above to ionizing radiation, for previous crosslinking and to already start sterilization;
 - after demolding of step (iii), coat the material with an outside layer, particularly of biocompatible polymeric material, optionally with the same polymeric material of item (i).
- 20

Particularly, the polymer of item (i) and the optional outside layer are made of polyorganosiloxane, more particularly polydimethylsiloxane.

25 A further object of the present invention is a method for the treatment of conditions or dysfunctions of the human body, characterized in that it uses the device as obtained according to the process described above, particularly as a subcutaneous implant. The device of the invention may also be used for the treatment of conditions or dysfunctions as an anal, vaginal, oral, nasal or any other insert.

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Below an example of use of the device of the present invention is presented, but its mention does not bring any limitation than the ones presented in the claims as further disclosed below.

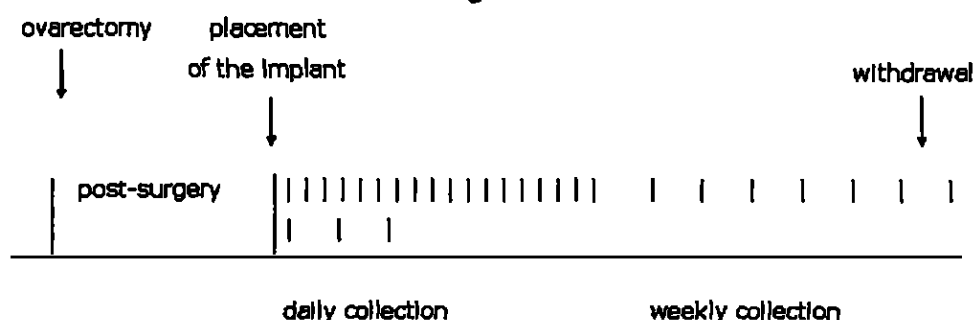
EXAMPLE

5 IN VIVO TEST

Cylindrically-shaped implants with 2 mm diameter and 20 mm long constituted by polydimethylsiloxane, 50 mg of 17 β -estradiol and barium sulfate as the radio marker were prepared. For Implant injection, Crestar[®] dischargeable heparinized syringes were used, and the blood should be obtained by means of venous puncture with a 25 x 8 needle.

An implant was subcutaneously injected in a mammal into its upper dorsal region, between pellets to facilitate application. That region was depilated.

Samples of blood from the mammal were collected a few days before inserting the implant and for a period of about 17 days after its placement. After this period, ten other samples were collected within weekly intervals. The sample as collected before the placement of the implant serves to confirm the non-existence of circulating estradiol.



The collected samples were centrifuged at 1000 rotations for 5 minutes. Supernatant (plasma) was separated and stocked at -20°C in Eppendorf tubes until assays were made. Subsequently, results of the samples corresponding to the average release of 17-β-estradiol during the assay period were plotted in a graph.

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29CLAIMS

1. HORMONE DELAYED RELEASE COMPOSITION, characterized in that it comprises a non-biodegradable biocompatible polymer matrix, crosslinked by ionizing radiation, wherein said matrix comprises one or
5 more hormones dispersed therein.
2. COMPOSITION, according to Claim 1, characterized in that said biocompatible polymer is chosen from polyorganosiloxanes, particularly polydialkylsiloxanes, such as polydimethylsiloxanes, and ethylene-vinyl acetate copolymer.
- 10 3. COMPOSITION, according to Claim 1, characterized in that said hormone is pharmaceutically acceptable, able to be delayed released by diffusion being dispersed within said polymeric matrix.
4. COMPOSITION, according to Claim 1, characterized in that said hormone is chosen among estrogens.
- 15 5. COMPOSITION, according to Claim 1, characterized in that said hormone is an estrogen, particularly β -estradiol.
6. COMPOSITION, according to Claim 1, characterized in that it contains up to about 80% by weight of inert fillers.
7. COMPOSITION, according to Claim 1, characterized in that
20 it contains a radio-opaque marker, particularly above 0.1% by weight, more particularly between 0.1% and 2%.
8. USE OF THE COMPOSITION, as described in Claims 1 to 7, characterized in that it is for the manufacture of a hormone delayed release device within the human body.
- 25 9. USE, according to Claim 8, characterized in that said device is a subcutaneous implant.
10. HORMONE DELAYED RELEASE DEVICE, within the human body, characterized in that it comprises the composition described

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Claims 1 to 7.

11. DEVICE, according to Claim 10, characterized in that it comprises an outside layer made of the same material of said polymeric matrix, or of a different material.

5 12. DEVICE, according to Claim 10, characterized in that said device presents geometry chosen from bands, sticks, cylinders or tubes.

13. DEVICE, according to Claim 12, characterized in that said device has the shape of a tube.

10 14. DEVICE, according to claim 12, characterized in that said device has the shape of an about 1 cm to about 12 cm long stick with about 0.3 mm to about 10 mm diameter.

15 15. DEVICE, according to claim 14, characterized in that said device has the shape of an about 1 cm to about 4 cm long stick with about 2 mm to about 4 mm diameter.

16. PROCESS FOR THE MANUFACTURE OF HORMONE DELAYED RELEASE DEVICE, within the human body, as described in Claims 10 to 15, characterized in that it comprises the steps of (i) mixing one or more substantially non-biodegradable biocompatible polymers with one or more hormones and additives, if any; (ii) cold molding said mixture into the desired
20 shape; (iii) cold de-molding; (iv) packing the obtained product; (v) exposing the packed product to enough ionizing radiation to crosslink the polymer and sterilize the packed product.

17. PROCESS, according to Claim 16, characterized in that said ionizing radiation is chosen between gamma radiation and beam of electrons.

25 18. PROCESS, according to Claim 16, characterized in that after the step (ii) of cold molding the mixture, the mixture is exposed to ionizing radiation.

19. PROCESS, according to Claim 16, characterized in that

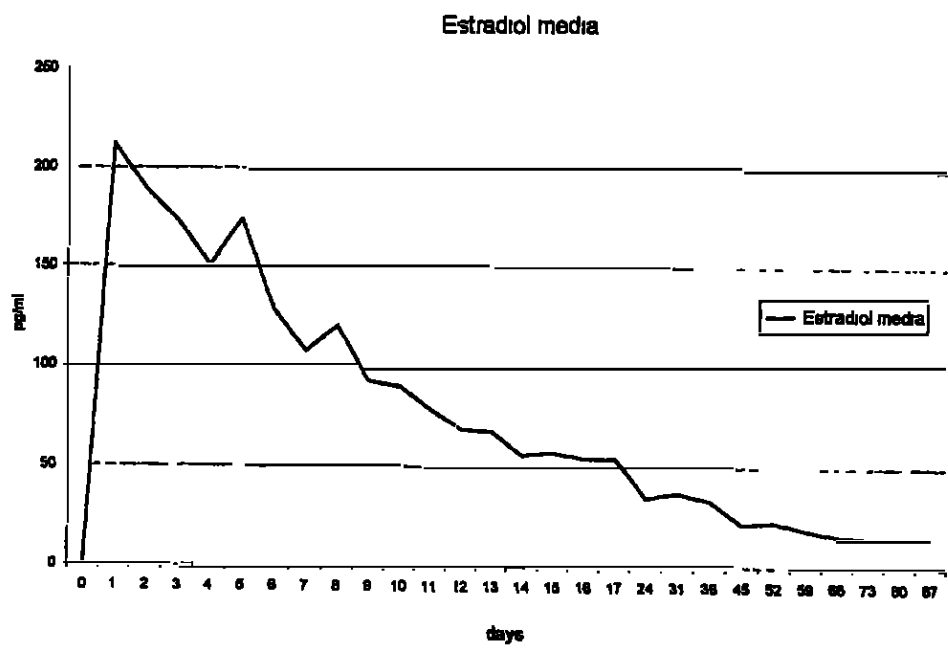
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after the step (iii) of cold demolding, the material is coated with an outside layer, particularly of biocompatible polymeric material, optionally the same polymeric material of item (i).

20. METHOD FOR THE TREATMENT OF CONDITIONS OR
5 DYSFUNCTIONS, of the human body, characterized in that it is by inserting and maintaining the composition as described in Claims 1 to 8, inside the human body for enough time for said hormone to be appropriately released within the body.

21. METHOD FOR THE TREATMENT OF CONDITIONS OR
DYSFUNCTIONS, of the human body, characterized in that it is by inserting and
10 maintaining the device as described in Claims 10 to 15, inside the human body for enough time for said hormone to be appropriately released within the body.

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INTERNATIONAL SEARCH REPORT

International application No
PCT/BR 2005/000183

A. CLASSIFICATION OF SUBJECT MATTER IPC⁷: A61K 9/02 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC⁷: A61K Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched — Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPODOC, PAJ		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
X	US 2004/0009222 A1 (CHOU et al.) 15 January 2004 (15.01.2004) <i>paragraphes [0012] and [0025], claims.</i> —	1, 2, 6, 10-19
X	US 4012497 A (SCHOPFLIN) 15 March 1977 (15.03.1977) <i>the whole document.</i> —	1, 2, 4-7, 10-12, 14, 15
X	EP 0970704 A1 (THE POPULATION COUNCIL, INC.) 12 January 2000 (12.01.2000) <i>the whole document.</i> —	1, 2, 6, 10-15
☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex		
* Special categories of cited documents "A" document defaming the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 5 December 2005 (05.12.2005)		Date of mailing of the international search report 20 December 2005 (20.12.2005)
Name and mailing address of the ISA/ AT Austrian Patent Office Dresdner Straße 87, A-1200 Vienna Facsimile No +43 / 1 / 534 24 / 535		Authorized officer KRENN M. Telephone No +43 / 1 / 534 24 / 435

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos
because they relate to subject matter not required to be searched by this Authority, namely
2. ☐ Claims Nos :
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically.
3. ☐ Claims Nos
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows.

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons

Claims Nos.: 20, 21 because they relate to subject matter not required to be searched by this Authority, namely:

Commonly, if claims are directed to a therapeutic method of treatment of the human/animal body, a search is carried out and based on the alleged effects of the composition. However, claims 20 and 21 do not refer to concrete technical features, e.g. a certain disease state making a search reasonable

Claims Nos.: 3, 8, 9 because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Claim 3 does not contain any concrete technical features.

The wording of claims 8 and 9 does not correspond to that required for second medical use claims (Use of composition X for the manufacture of a medicament for treating Y); thus it is not clear, for what protection is sought for in said claims.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees

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INTERNATIONAL SEARCH REPORT

Information on parent family members

International application No
PCT/BR 2005/000183

Patent document cited in search report			Publication date		Patent family member(s)		Publication date	
EP	A	970704			PT	T	970704T	2003-01-31
					JP	A	2000044489	2000-02-15
					HU	A2	9902225	2002-01-28
					ES	T3	2186280T	2003-05-01
					EP	A1	0970704	2000-01-12
					DK	T3	970704T	2003-01-20
US	A	20040009222					none	
US	A	4012497			JP	A	51061618	1976-05-28
					ZA	A	7506082	1976-09-29
					PL	A1	183556	1978-04-24
					NL	A	7511244	1976-03-26
					FR	A1	2285895	1976-04-23
					DK	A	428175	1976-03-25

PATENT COOPERATION TREATY

36 36

To:

CELIDONIO Ana Paulo S.
Av. Brigadeiro Faria Lima, 1485
Torre Norte - 12th floor
01452-002 Sao Paulo
Brazil

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing 20 December 2005 (20.12.2005)
(day/month/year)

Applicant's or agent's file reference
1046-0005

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/BR 2005/000183

International filing date (day/month/year)
9 September 2005 (09.09.2005)

Priority Date (day/month/year)
9 September 2004 (09.09.2004)

International Patent Classification (IPC) or both national classification and IPC
A61K 9/02

Applicant

BIOLAB SANUS FARMACÉUTICA LTDA.

1. This opinion contains indications relating to the following items:

- ☒ Cont. No. I Basis of the opinion
☐ Cont. No. II Priority
☒ Cont. No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐ Cont. No. IV Lack of unity of invention
☒ Cont. No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐ Cont. No. VI Certain documents cited
☒ Cont. No. VII Certain defects in the international application
☐ Cont. No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66 I bis(b) that written opinions of this International Searching Authority will not be so considered

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ AT
Austrian Patent Office
Dresdner Straße 87, A-1200 Vienna
Facsimile No. +43 / 1 / 534 24 / 535

Authorized officer
KRENN M.
Telephone No. +43 / 1 / 534 24 / 435

Continuation No. I

Basis of the opinion

1. With regard to the language, this opinion has been established on the basis of

Continuation No. III:

**Non-establishment of opinion with regard to
novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of the said claims Nos. 3, 8, 9, 20, 21 because said claims Nos. 20, 21 relate to the following subject matter which does not require an international preliminary examination (specify):

Commonly, if claims are directed to a therapeutic method of treatment of the human/animal body, an examination is carried out and bases on the alleged effects of the composition. However, claims 20 and 21 do not refer to concrete technical features, e.g. a certain disease state making an examination reasonable.;

the description, claims or drawings (particular elements indicated below) or said claims Nos. 3, 8, 9 are so unclear that no meaningful opinion could be formed (specify):

Claim 3 does not contain any concrete technical features.

The wording of claims 8 and 9 does not correspond to that required for second medical use claims (Use of composition X for the manufacture of a medicament for treating Y); thus it is not clear, for what protection is sought for in said claims.;

no international search report has been established for said claims Nos. 3, 8, 9, 20, 21

Continuation No. V

**Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step
or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims —	YES
	Claims 1, 2, 4-7, 10-19	NO
Inventive step (IS)	Claims —	YES
	Claims 1, 2, 4-7, 10-19	NO
Industrial applicability (IA)	Claims 1, 2, 4-7, 10-19	YES

2. Citations and explanations:

US 2004/0009222 A1 describes implantable drug delivery devices comprising an inner steroid-containing core and an outer polymeric skin, e.g. ethylene vinyl acetate. Curing of the polymeric material is preferably effectuated by radiation to prevent the active agent from damage.

The subject matter of US 4012497 A is an optionally coated sustained release pharmaceutical composition for steroids, e.g. ethinylestradiol on the basis of organopolysiloxane. The composition may additionally contain barium sulphate to improve X-ray localization in the body.

EP 970704 A1 refers to a silicone core long term androgen delivery implant additionally providing a coating of ethylene vinyl acetate. The implant is preferably in the form of a hollow cylinder.

In respect to the above cited documents claims 1, 2, 4-7 and 10-19 is neither new nor inventive. The manufacturing process described in claims 18-19 is only anticipated by US 2004/0009222 A1, which is the only document referring to a curing process by radiation.

Industrial applicability is given for claims 1, 2, 4-7 and 10-19.

Claims 3, 8, 9, 20, 21: see "Certain claims were unsearchable".

Continuation No. VII:

Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

The non-biodegradable biocompatible polymer (claim 1) is considered to be an essential feature of the present invention; thus it needs to be specified in a structural manner. "Crosslinked by ionizing radiation.." (claim 1) represents a process step, which is not suitable for characterizing a product. Consequently, said feature was not considered in establishing the present report.

The formulation "...within the human body.." (claim 10) should be deleted, because protection can only be sought for a product and not for the target area in the human body.

The formulation "...or a different material." (claim 11) is insufficiently precise. It should be either specified or deleted.

The term "about" may not be used in connection with numerical ranges (claims 14,15).

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 1046-0005	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/BR 2005/000183	International filing date (day/month/year) 9 September 2005 (09.09.2005)	(Earliest) Priority Date (day/month/year) 9 September 2004 (09.09.2004)
Applicant BIOLAB SANUS FARMACEUTICA LTDA.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 5 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see continuation of this first sheet

2 ☒ Certain claims were found unsearchable (see continuation of this first sheet)

3. ☐ Unity of invention is lacking (see continuation of this first sheet)

4. With regard to the title,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

Hormone delayed release composition on the basis of polyorganosiloxanes or ethylene vinyl acetate resp. process for its manufacture.

5. With regard to the abstract,

☐ the text is approved as submitted by the applicant.

☒ the text has been established, according to Rule 35.2(b), by this Authority as it appears in the continuation of this first sheet. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6 With regard to the drawings,

a. the figure of the drawings to be published with the abstract is Figure No. ____

☐ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☐ none of the figures is to be published with the abstract.

Continuation of first sheet

Continuation No.II:

Observations where certain claims were found unsearchable

(Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

Claims Nos.: 20, 21 because they relate to subject matter not required to be searched by this Authority, namely:

Commonly, if claims are directed to a therapeutic method of treatment of the human/animal body, a search is carried out and bases on the alleged effects of the composition. However, claims 20 and 21 do not refer to concrete technical features, e.g. a certain disease state making a search reasonable.

Claims Nos.: 3, 8, 9 because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Claim 3 does not contain any concrete technical features.

The wording of claims 8 and 9 does not correspond to that required for second medical use claims (Use of composition X for the manufacture of a medicament for treating Y); thus it is not clear, for what protection is sought for in said claims.

Continuation No. IV:

Text of the abstract

(Continuation of item 5 of the first sheet)

"Hormone delayed release composition, use of the composition, hormone delayed release device, process for the manufacture of hormone delayed release device and methods for the treatment of conditions or dysfunctions"

The present invention refers to a hormone delayed release composition within the human body, more particularly to a non-biodegradable biocompatible composition comprising a

polymer matrix selected from the group of polyorganosiloxanes or ethylene vinyl acetate crosslinked by ionizing radiation wherein a hormone is dispersed. In other aspects, the present invention refers to the use of said composition to obtain hormone delayed release device, to the process for the manufacture of said device and to a method for the treatment of conditions or dysfunctions of the human body.

A. CLASSIFICATION OF SUBJECT MATTER IPC ⁷ : A61K 9/02 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC ⁷ : A61K Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched --- Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPODOC, PAJ		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category ^a	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2004/0009222 A1 (CHOU et al.) 15 January 2004 (15.01.2004) <i>paragraphes [0012] and [0025], claims.</i> ---	1, 2, 6, 10-19
X	US 4012497 A (SCHOPFLIN) 15 March 1977 (15.03.1977) <i>the whole document.</i> ---	1, 2, 4-7, 10-12, 14, 15
X	EP 0970704 A1 (THE POPULATION COUNCIL, INC.) 12 January 2000 (12.01.2000) <i>the whole document.</i> ---	1, 2, 6, 10-15
☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
^a Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search 5 December 2005 (05.12.2005)		Date of mailing of the international search report 20 December 2005 (20.12.2005)
Name and mailing address of the ISA/ AT Austrian Patent Office Dresdner Straße 87, A-1200 Vienna Facsimile No. +43 / 1 / 534 24 / 535		Authorized officer KRENN M. Telephone No. +43 / 1 / 534 24 / 435

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/BR 2005/000183

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Patent document cited in search report			Publication date		Patent family member(s)		Publication date	
EP	A	970704			PT	T	970704T	2003-01-31
					JP	A	2000044489	2000-02-15
					KU	A2	9902225	2002-01-28
					ES	T3	2186280T	2003-05-01
					EP	A1	0970704	2000-01-12
					DK	T3	970704T	2003-01-20
US A 20040009222			none					
US	A	4012497			JP	A	51061618	1976-05-28
					ZA	A	7506082	1976-09-29
					PL	A1	183556	1978-04-24
					NL	A	7511244	1976-03-26
					FR	A1	2285895	1976-04-23
					DK	A	428175	1976-03-25

Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT

PATENTE DE INVENCION

☒

MODELO DE UTILIDAD ☐

- ◆ Indicación de que se solicita la concesión de una patente ☒
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud ☒
- ◆ Descripción de la invención ☒
- ◆ Dibujos de ser estos pertinentes ☐
- ◆ Comprobante de pago de las tasas establecidas ☒

COMPLETA ☐

INCOMPLETA ☐

DISEÑO INDUSTRIAL ☒

- ◆ Indicación de que se solicita el registro de Diseño Industrial ☐
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud ☐
- ◆ Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño ☐
- ◆ Comprobante de pago de las tasas establecidas ☐

COMPLETA ☐

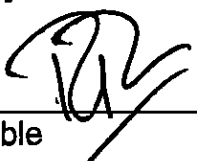
INCOMPLETA ☐

ESQUEMA DE TRAZADO ☐

- ◆ Indicación de que se solicita el registro de un Esquema de Trazado ☐
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud ☐
- ◆ Representación gráfica del esquema trazado ☐
- ◆ Comprobante de pago de las tasas establecidas ☐

COMPLETA ☐

INCOMPLETA ☐

Firma Responsable 

Fecha _____

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