

OPOS



Industria y Comercio
SUPERINTENDENCIA

Delegatura de propiedad Industrial
División de Nuevas Creaciones

PCT

SOLICITUD
PATENTE DE INVENCION

21. EXPEDIENTE No. 04-60435

54. TÍTULO Regimen de Dosificacion y composicion Farmaceutica
para Anticoncepcion de Emergencia

51. CLASIFICACIÓN INTERNACIONAL _____

71. SOLICITANTE Richter Gedeon Vegyeszeti Gyár RT

DOMICILIO Budapest, Hungría

74. APODERADO Alvaro Correa Odonez
T.P 20281

22. BOGOTÁ, D. C., Junio 25 de 2004

PETITORIO

Industria y Comercio
SUPERINTENDENCIA

Superintendencia y Comercio
Radicación: 04060435 00000000 Folios: 51
Fecha (ADM): 2004-06-25 16:16:45
Trámite: 011 PCT-PATENT 379 FASE NACI 411 PRESENTA
Dependencia: 2000 DIVISION DE NUEVAS CREACIONES

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.

② SOLICITANTE (71)

Nombre: RICHTER GEDEON VEGYÉSZETI GYÁR RT.	IDENTIFICACION C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número _____
Dirección: Gyömrői út 19-21, H-1103 Budapest, Hungría	
Nacionalidad o Domicilio: HUNGARO	
Lugar de Constitución: BUDAPEST, HUNGRIA	
Teléfono: _____ Fax: _____ E-Mail: _____	

③ REPRESENTANTE O APODERADO

Nombre: ALVARO CORREA ORDOÑEZ	IDENTIFICACION C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número 79.143.366 de Usaquén TP 20.281
Dirección: Avenida 82 No. 10-62 Piso 6	
Teléfono: 634-1500 Fax: 376-2211	
E-Mail: patents.bogota@bakernet.com	

④ INVENTOR (ES) (72)

Nombre: VER ANEXO
Dirección: VER ANEXO
Nacionalidad o Domicilio: VER ANEXO

⑤ PCT (85)

Solicitud Internacional No. PCT/HU02/00129	Fecha Noviembre 26, 2002
Publicación Internacional No. WO 03/045397	Fecha Junio 5, 2003

⑥ Título (54) RÉGIMEN DE DOSIFICACIÓN Y COMPOSICIÓN FARMACÉUTICA PARA ANTICONCEPCIÓN DE EMERGENCIA.

⑦ Clasificación Internacional (51) A61K 31/565

⑧ Prioridad SI ☒ NO ☐	(33) País de Origen HU	(32) Fecha Noviembre 27, 2001	(31) Número de Solicitud P01 05173
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⑨ Comprobante de pago No. 04-27,078 Fecha ABRIL 2 DE 2004

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

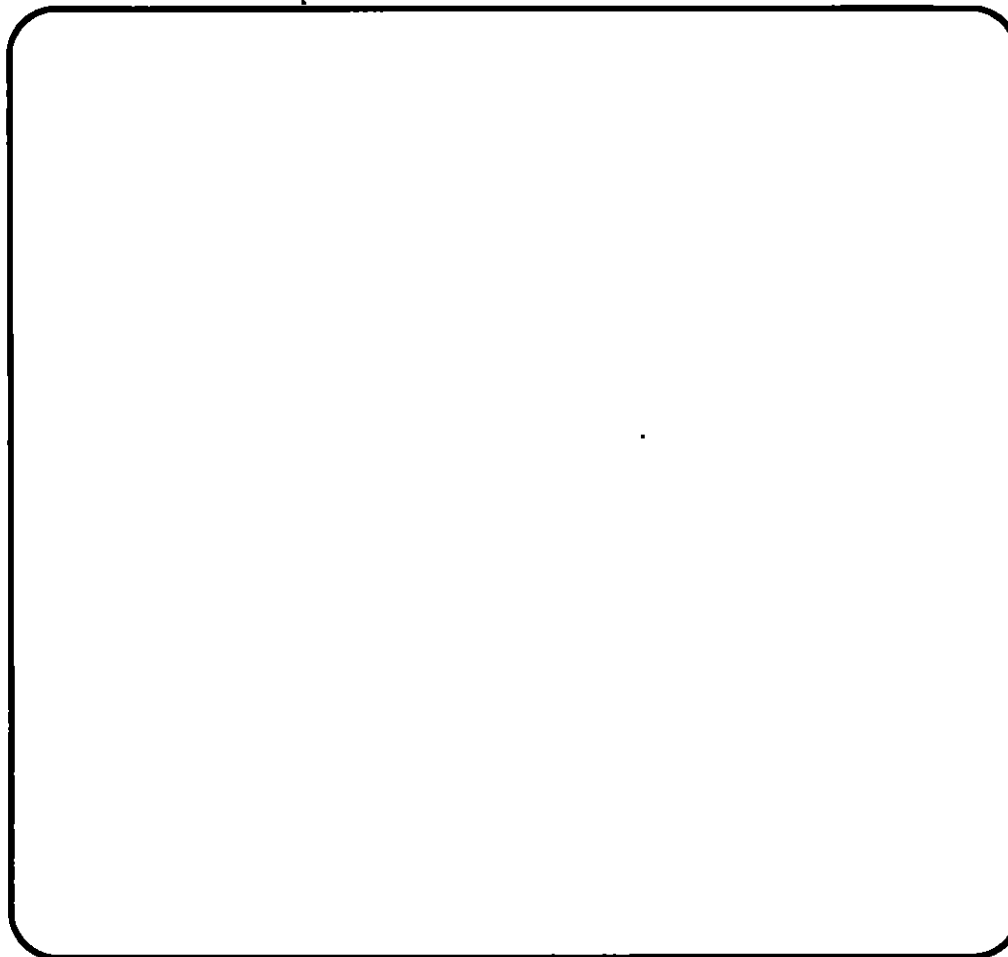
10

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 12 x 12
- ☐ 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

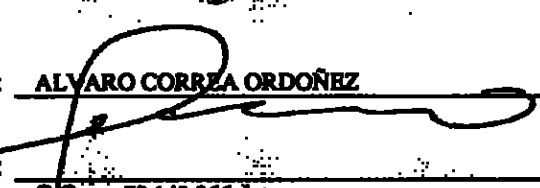
11

FIGURA CARACTERISTICA



12

Solicito la concesión de la patente,

NOMBRE: ALVARO CORREA ORDOÑEZFIRMA: C.C. 79.143.366 de
Uruquén

T.P. 20.281

10443

Radicación : 04860435 00000000 Folios: 51
Fecha (HH): 2004-06-25 16:16:45
Tramite : 011 PCT-PATENT 379 FASE MACI 411 PRESENTA
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 04 - 27,078
FECHA : ABRIL 2 DE 2004

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PBO	PAGO
ALVARO CORREA ORDONEZ	CONSIGNACION	BANCO POPULAR	050-00110-6	20331067	02/04/2004	137,305,000.00

***** CONCEPTO *****

CANT. CONTABILISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	422,000.00
	TOTAL :	422,000.00

SON: CUATROCIENTOS VEINTIDOS MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

ANEXO - INVENTORES

TITULO: RÉGIMEN DE DOSIFICACIÓN Y COMPOSICIÓN FARMACÉUTICA PARA ANTICONCEPCIÓN DE EMERGENCIA.

Nombre:	<u>VAN LOOK, Paul, F., A.</u>
Dirección:	<u>Avenue Appia 20,</u> <u>CH-1211 Geneva 27</u>
Nacionalidad ó Domicilio:	<u>SUIZA</u>
Nombre:	<u>BALOGH, Illésné</u>
Dirección:	<u>Gárdonyi u. 11.,</u> <u>H-1222, Budapest</u>
Nacionalidad ó Domicilio:	<u>HUNGRIA</u>
Nombre:	<u>KOMÁNDI, Katalin</u>
Dirección:	<u>Bertan Lajos u. 24.,</u> <u>H-1111, Budapest</u>
Nacionalidad ó Domicilio:	<u>HUNGRIA</u>

5

WO 03/045387

PCT/HU02/00129

Nombre:	<u>NEMES, László</u>
Dirección:	<u>Bonyhádi u. 98.,</u> <u>H-1141, Budapest</u>
Nacionalidad ó Domicilio:	<u>HUNGARO</u>
Nombre:	<u>SZABÓ, Zsolt</u>
Dirección:	<u>Csalogány u. 33.,</u> <u>H-2141, Csömör</u>
Nacionalidad ó Domicilio:	<u>HUNGARO</u>

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TRADUCCIÓN OFICIAL N° 200204 de un documento escrito en inglés, efectuada el día 20 de febrero de 2004 por Jaime Armando Garavito Burgos, c.c. N° 19.130.702 de Bogotá, Traductor Oficial según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia

Poder otorgado por Richter Gedeon Gyegyszeti Gyar Rt.

Texto en inglés y en español mediante el cual **Richter Gedeon Gyegyszeti Gyar Rt.**, domiciliada **H-1103 Budapest, Gyomroi út 19-21, Hungría**, otorga poder a **ALVARO CORREA ORDOÑEZ y/o OLGA GEORGETTE OTERO y/o RICARDO METKE y/o JUAN PABLO CONCHA DELGADO**

Dado y suscrito en Budapest, el día 05 de febrero de 2004

(firmado) Dr. Polgar István. Director Propiedad Intelectual

(firmado) TALIGÁS Beáta, Gerente, International, Dosage Form Products

Jaime A. Garavito B
JAIME A. GARAVITO B

TRADUCTOR E INTERPRETE OFICIAL
Res 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA

CERTIFICACIÓN NOTARIAL

A los 05 días del mes de febrero de 2004, el suscrito Notario

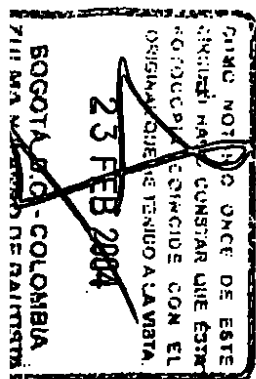
DA FE

1. Que Dr. POLGAR István y TALIGAS Beáta, mayores y domiciliado en H-1026 Budapest, Torokvés, lejtó 2., Hungría H-1173 Budapest, 517. u. 5, suscribió de su puño y letra el documento que antecede.
2. Que conozco al otorgante y que éste tiene capacidad legal para el otorgamiento.
3. Que el otorgante ha suscrito el referido documento en su carácter de Director, Propiedad Intelectual, Gerente Internacional de la persona jurídica **Richter Gedeon Vegyészeti Gyár Rt.**

Que la persona jurídica **Richter Gedeon Vegyészeti Gyár Rt.** tiene sede en **H-1103 Budapest, Gyömroi út 19-21., Hungría**, está legalmente constituida, que tiene existencia legal actual y que el acto para el cual se otorga la cesión está comprendido entre los que constituyen su objeto social.

Que el otorgante tiene efectivamente la representación que ostenta y que ésta es legítima.

6. Que he basado las certificaciones 3, 4 y 5 anteriores en los siguientes documentos auténticos que al efecto se me exhibieron y que menciono específicamente con expresión de sus fecha y de su origen o procedencia:



7
-2 7

**Extracto de Registro Comercial expedido por la Corte Metropolitana como Corte que
lleva registro de sus actuaciones el 02 de febrero de 2004**

Licencia inglesa N°: IM/IGKOD/2003/KÖZJ/937
Archivo N°: 6026-6027/2004.

Por medio del presente certifico que el "PODER" anexo ha sido firmado en mi presencia por
encima de sus nombres respectivamente por _____ **Dr. POLGÁR**

István (segundo apellido: Weisz Rózsa, domiciliado en H-1026 Budapest, Törökvész lejtő 2.
/Hungria/) quien estableció su identidad exhibiendo su tarjeta de identidad húngara N° AU-

VI.696705 y por _____ **TALIGÁS Beáta** (segundo apellido:
Végh Erzsébet, domiciliado en H-1173 Budapest, 517. utca 5. /Hungria/), quien estableció su
identidad exhibiendo su tarjeta de identidad húngara N° AN317115.

Ambas personas son signatarios debidamente autorizados de la compañía **Richter Gedeon
Vegyészeti Gyár Rt.** (sede registrada: H-1103 Budapest, Gyömrői út 19-21., número de registro:
Cg. 01-10-040944), una sociedad registrada y existente de acuerdo con las leyes y reglamentaciones
húngaras y la cual se encuentra involucrada en actividades compatibles con sus fines sociales.

Budapest, febrero 5 del año 2004 (dos mil cuatro).

(firmado) dr. Komáromi József, Notario Civil Sustituto

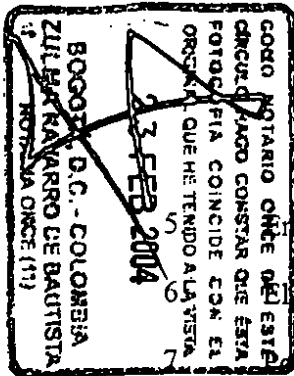
(Aparece sello en tinta azul)

Jaime A. Garavito B.
JAIME A. GARAVITO B.

TRADUCTOR E INTERPRETE JURADO
Res. 034 de Enero 11 de 1993
MINISTERIO DE JUSTICIA

APOSTILLA

1. País: República de Hungría
Este documento público
2. Ha sido firmado por dr. Komáromi József
3. Quien actúa en calidad de (palabra en Húngaro)
4. Lleva el sello de (Texto en húngaro: "dr.Fullér Kriztina budapesti Közjegyző")



Certificado

Budapest

(fecha en húngaro)

el Ministro de Justicia de la República de Hungría

8. N° IM/NEMZ/2004/HIT 1/1095

9. Sello (Sello redondo en tinta azul del Ministerio de Justicia de la República de Hungría)
10. Firma (firma ilegible) Dr. Szöcs Tibor (Debajo aparece palabra en húngaro)

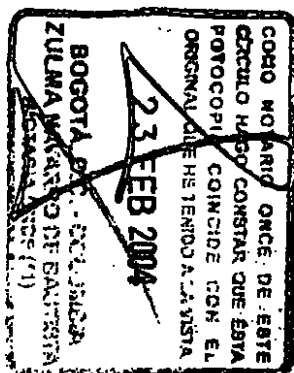
La anterior es traducción fiel y completa de la cual se deja copia en esta oficina para su confrontación.

Jaime A. Garavito B.

Jaime Armando Garavito Burgos
c.c. N° 19.130.702 de Bogotá

Traductor e Intérprete Oficial según Resolución N° 034 de enero 11 de 1983 expedida por el Ministerio de Justicia

Jaime A. Garavito B.
JAIME A. GARAVITO B
TRADUCCION E INTERPRETE OFICIAL
Res 034 de Enero 11 de 1983
MINISTERIO DE JUSTICIA



9

POWER OF ATTORNEY

PODER

The undersigned.

La abajo firmada.

RICHTER

GEDEON

GEGYÉSZETI

Richter Gedeon Vegyészeti Gyár Rt.

GYÁR RT.

Name of the Company

Nombre de la Compañía

H-103 Budapest, Gyömrői út 19-21., Hungary

domiciled in

Address, city, country

domiciliada en

Dirección, ciudad, país

H-103 Budapest, Gyömrői út 19-21.,
Hungria

declares that it hereby grants to

declara por el presente otorgar a

ALVARO CORREA-ORDOÑEZ and/or OLGA
GEORGETTE OTERO and/or RICARDO METKE
and/or JUAN PABLO CONCHA

ALVARO CORREA-ORDOÑEZ y/o OLGA
GEORGETTE OTERO y/o RICARDO METKE y/o
JUAN PABLO CONCHA

with domicile at Av. 82 No. 10-82, 6th floor, of Bogotá
D.C., Colombia, a full and sufficient power of attorney
to obtain the protection of

con domicilio en la Av. 82 No. 10-82 Piso 6 en Bogotá
D.C., Colombia, poder especial amplio y suficiente,
para obtener la protección de:

my (our) Industrial property and against the unfair
competition, for which purpose I (we) authorize the said
attorneys to represent me (us) before any authorities or
persons; with or without jurisdiction, especially those
administrative, administrative contentious and judicial,
as well as before Arbitration Court, in all matters
concerning the following: a) Obtaining of patents,
utility models, industrial designs, integrated circuits
layout designs and vegetal varieties; the registration of
trademarks, denominations of origin, commercial
names, trade emblems, slogans and domain names; its
renewal, assignment, change of name or domicile,
voluntary cancellation; and the registration of licenses
of use of the above rights; b) Processes of protection to
the consumer, unfair competition, oppositions,
cancellations, nullity, precautionary injunctions,
infringement, granting of licenses, writ mandamus, the
protection of trade secrets, and in general the civil,
penal, and administrative processes relating to those
rights. And that in all the above matters they may
substitute this Power of Attorney, compromise,
conciliate, admit the facts of the case, desist, cancel,
receive, resign, and ratify acts done by representatives
without a power of attorney.

mi (nuestra) propiedad Industrial y contra la
competencia desleal, a cuyo efecto autorizo (amos) a
los dichos apoderados para que me (nos) representen
ante cualesquiera autoridades o personas, ejerzan o no
jurisdicción, especialmente ante las del orden
administrativo, contencioso administrativo y judicial,
así como los tribunales de arbitramento, en todo lo
concerniente a los siguientes asuntos: a) Obtención de
patentes de invención, modelos de utilidad, diseños
industriales, esquemas de trazado de circuitos
integrados y variedades vegetales; el registro de
marcas, denominaciones de origen, nombres
comerciales, enseñas, lemas comerciales y nombres
de dominio; su renovación, traspaso, cambio de
nombre o domicilio, cancelación voluntaria; y el registro
de licencias de uso de esos derechos; b) Los procesos
para la protección del consumidor, competencia
desleal, oposiciones, cancelaciones, nulidades,
medidas cautelares, infracciones, concesión de
licencias, la tutela, la protección de secretos
industriales, y en general procesos civiles, penales,
administrativos relacionados con estos derechos. Y
para que en todos los asuntos arriba determinados,
puedan sustituir este mandato, transigir, conciliar,
admitir los hechos del caso, desistir, cancelar, recibir,
renunciar, y ratificar los actos de agentes oficiosos.

I hereby ratify all actions previously taken on behalf of
this company by the aforementioned attorneys with
respect to the mentioned matters.

Iguualmente, ratifico todo lo actuado hasta el momento
en los mismos asuntos, por cualquiera de los
mencionados apoderados en representación de ésta
sociedad.

Done and subscribed in Budapest

Dado y firmado en Budapest

On the 5th day of February of 2004

A los 5 días del mes de Febrero de 2004

Dr. FOLGAR Is

Director

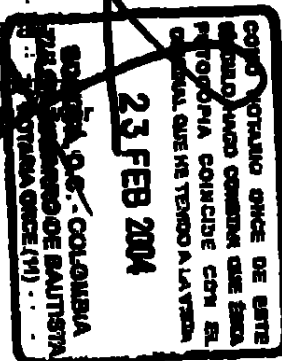
Intellectual Property

Signature of the person issuing the

TALIGAS Beata

Manager

International, Dosage Form Products
Firma de la persona que firma el Poder



NOTARIAL CERTIFICATION

CERTIFICACION NOTARIAL

this 5th day of February

A los 5 días del mes de Febrero

of the undersigned Notary

de 2003, el suscrito Notario

CERTIFIES

DA FE

That 1) Dr. POLGÁR István
2) TALIGÁS Beáta

1. Que Dr. POLGÁR István
TALIGÁS Beáta

of legal age and domiciled in

mayor y domiciliado en

1) H-1026 Budapest, Törökvez lejtő 2., Hungary
2) H-1173 Budapest, 517. u. 5.

H-1026 Budapest, Törökvez lejtő 2., Hungria
H-1173 Budapest, 517. u. 5

set his hand on the foregoing document.

suscribió de su puño y letra el documento que antecede.

That the grantor is to me personally know and that he/she has legal capacity to execute the instrument.

2. Que conozco al otorgante y que éste tiene capacidad legal para el otorgamiento.

That the grantor has executed the foregoing document as

3. Que el otorgante ha suscrito el referido documento en su

1) Director, Intellectual Property
2) Manager International, Dosage Form Products

capacidad de Director, Propiedad Intelectual
Gerente Internacional

of the judicial person

de la persona jurídica

Richter Gedeon Vegyészeti Gyár Rt.

Richter Gedeon Vegyészeti Gyár Rt.

That the judicial person

4. Que la persona jurídica

Richter Gedeon Vegyészeti Gyár Rt.

Richter Gedeon Vegyészeti Gyár Rt.

having its home office in

con sede en

H-1103 Budapest, Gyömrői út 19-21., Hungary

H-1103 Budapest, Gyömrői út 19-21.,
Hungria

is duly organized, has present legal existence and that the purposes for which the power of attorney is granted are within the scope of its corporate purposes.

está legalmente constituida, que tiene existencia legal actual y que el acto para el cual se ha otorgado el poder está comprendido entre los que constituyen su objeto social.

5. That the grantor has in fact the referred to authority and that his/her representation is legal.

5. Que el otorgante tiene efectivamente la representación que ostenta, y que esta es legítima.

6. That I have based certifications 3, 4 and 5 above on the following authentic documents for such purpose exhibited to me and which I mention specifically, giving their dates and their origin or source:

6. Que he basado las certificaciones 3, 4 y 5 anteriores en los siguientes documentos auténticos que al efecto se me exhibieron y que menciono específicamente con expresión de sus fechas y de su origen o procedencia:

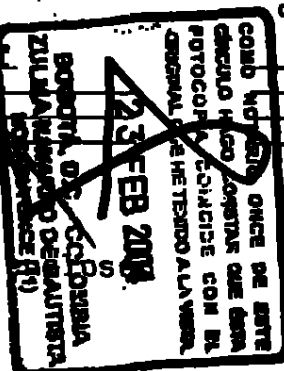
Trade Register Extract issued by
the Metropolitan Court as Court of
Registration on 2nd February 2004

Extracto de Registro comercial
expedido por la Corte Metropoli
na como corte que lleva registr
de sus actuaciones el 2 de
febrero de 2004

Notary Public

El Notario Público

Notarial certification

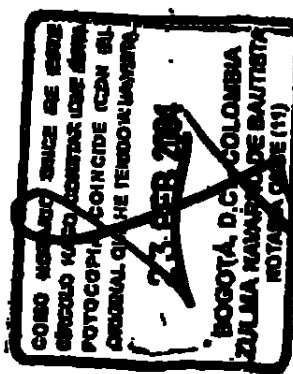




dr. Fullér Krisztina közjegyző

Budapest XIV., Szobránc u. 1. - 1581 Budapest, Pf. 44.- Telefon: 467-0320, 467-0323 - Fax: 467-0325

English Licence No.: IM/IGKOD/2003/KÖZI/937.
File No.: 6026-6027/2004.



---I hereby certify that the "POWER OF ATTORNEY" attached has been signed in my presence above their name respectively by -----

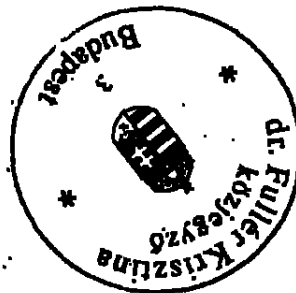
- Dr. POLGÁR István (mother's maiden name: Weisz Rózsa, domiciled at H-1026 Budapest, Törökvész lejtő 2. /Hungary/) who established his identity by his Hungarian identity card N^o AU-VI.696705, and by -----

- TALIGÁS Beáta (mother's maiden name: Végh Erzsébet, domiciled at H-1173 Budapest, 517. utca 5. /Hungary/), who established her identity by her Hungarian identity card N^o AN317115. -----

Both persons are duly authorised signatory of the company Richter Gedeon Vegyészeti Gyár Rt. (registered seat: H-1103 Budapest, Gyömrői út 19-21., registration number: Cg. 01-10-040944), a company registered and existing according to the Hungarian laws and regulations, and which is engaged in activities compatible with its corporate purposes. -----

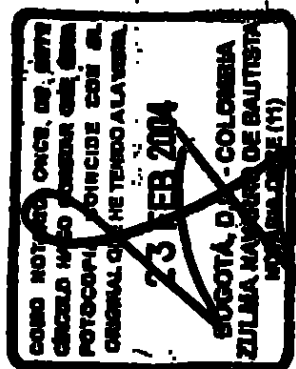
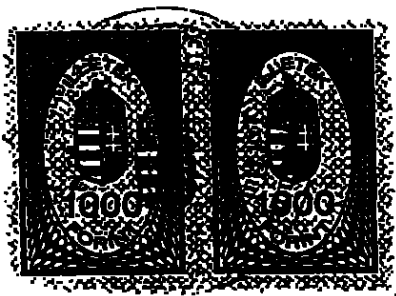
---Budapest this 5th (fifth) day of February in the year of 2004 (two thousand and four) -----


dr. Kónya István
Civil Law Notary Substitute



COMO INCALZAR DALLA DE ESTE
CIRCUITO N. 100 (CANTAL) CHE ESTE
FOTOCOPIA CONFINDE CON SUO
ORIGINAL CHE SE TENDO LA VERBA
23 FEB 2004
REGOTA D.C. COLOMBIA
ZILMIA SARABO DE SAUTISTA
NOTA (Cant. 11)





13

APOSTILLE
(Convention de la Haye du 5 octobre 1961)

1. Ország: **MAGYAR KÖZTÁRSASÁG**
Pays: **RÉPUBLIQUE DE HONGRIE**
Country: **REPUBLIC OF HUNGARY**

Est a közokiratot
Le présent acte public
This public document

2. Írta alá: **dr. Komáromi József**
a été signé par: _____
has been signed by:

3. minőségben eljárva: **közjegyzőhelyettes**
agissant en qualité de: _____
acting in the capacity of

4. Az okirat pecsétjével
(bélyegzőlelenyomattal) van ellátva **dr. Fullér Krisztina budapesti közjegyző**
est revêtu du (timbre de) _____
bears the seal/stamp of

Tanúsítja
Atteste
Certified

5. helység: **Budapest**
à _____
at

6. időpont: év **2004.** hónap **február** nap **11.**
le: (an) (mois) (jour)
date (year) (month) (day)

7. kiállítás: **A MAGYAR KÖZTÁRSASÁG IGAZSÁGÜGYI MINISZTERIUMA**
par: **LE MINISTRE DE LA JUSTICE DE LA RÉPUBLIQUE DE HONGRIE**
by: **MINISTRY OF JUSTICE OF THE REPUBLIC OF HUNGARY**

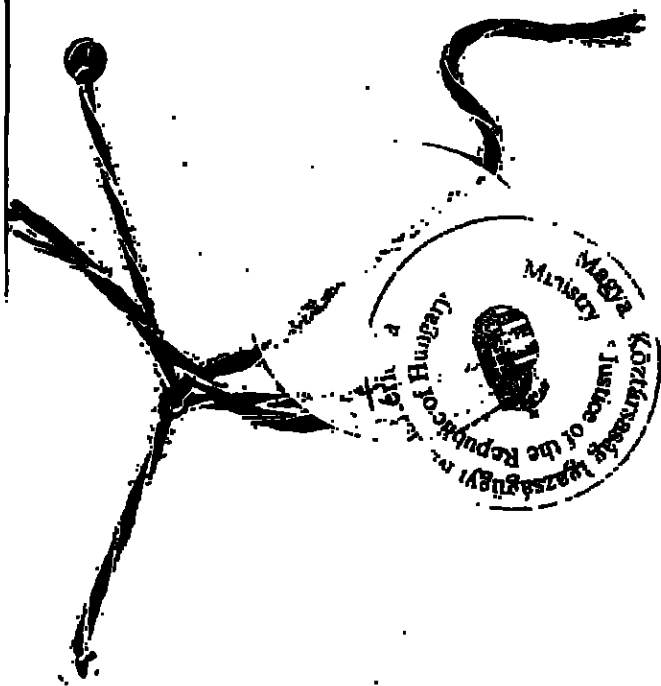
8. Ügyszám: **IM/NEMZ/2004/HIT 1/1095.**
Sous No.: _____
No.:

9. Pecsét (bélyegzőlelenyomattal): **Ministry of Justice of the Republic of Hungary**
Seal/stamp: _____
10. Alírás: **Dr. Szócs Tibor**
Signature: **osztályvezető**



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(54) Title: DOSAGE REGIMEN AND PHARMACEUTICAL COMPOSITION FOR EMERGENCY CONTRACEPTION

(57) Abstract: The invention relates to a dosage regimen for emergency contraception, to pharmaceutical compositions of the same purpose, to the use of levonorgestrel for the manufacture of pharmaceutical compositions for the same purpose, as well as to the manufacturing process of these pharmaceutical compositions. According to the invention the emergency contraception carried out by the use of levonorgestrel as active ingredient is characterised by administering a single application dose containing 1.5 ± 0.2 mg of levonorgestrel as active ingredient up to 72 hours after the coitus. The pharmaceutical compositions for emergency contraception according to the invention contain only 1.5 ± 0.2 mg of levonorgestrel as active ingredient in each application dose in admixture with known excipients, diluents, flavoring or aromatizing, stabilizers, as well as formulation-promoting or formulation-providing additives, commonly used in the pharmaceutical practice.

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Dosage regimen and pharmaceutical composition for emergency contraception

This invention relates to a dosage regimen for emergency contraception, to pharmaceutical compositions of the same purpose, the use of levonorgestrel for the manufacture of pharmaceutical compositions for the same purpose, as well as the process of manufacturing these pharmaceutical compositions.

It is known that coitus takes place in numerous cases, when conception must be prevented by all means. Several devices and pharmaceutical compositions are available for the prevention of undesirable conception in the case of regular and planned coitus. For example, condom, pessary, intrauterine devices as well as the different mono-or multi-phasic oral contraceptives.

But in the case of non-planned coitus or coitus with imperfect contraception these devices are not available or only in inadequate way, therefore precautions for preventing conception must be taken after the coitus. Such is the situation for example in the case of women, who have non-regular sexual life or the victims of rapes, or if the device for preventing conception, for example the condom, gets damaged or torn. Since in these cases the contraception must be achieved before the implantation of the fertilized egg— in relatively short time — these methods are called emergency contraception.

Norgestrel and levonorgestrel, namely the D isomer of norgestrel [$\pm$ -17 α -13-ethyl-17-hydroxy-18,19-dinorpregn-4-en-20-in-3-on] have been used in combined preparations as contraceptives for a long time. For example a pharmaceutical composition called OVRAL, which appeared in 1968 and contained 0.05 mg of ethynyl-estradiol and 0.5 mg of norgestrel. The British patent No 1,041,280 describes the preparation of tablets, capsules and suspension of anabolic activity containing 5 mg of norgestrel as active ingredient, although in the description of the biological activity of the active ingredient the estrogen antagonist activity is said to be 53.7-fold compared to that of the progesterone and the progestogen activity is the same as that of the progesterone.

In the 1970's comprehensive studies were carried out [The Journal of Reproductive Medicine, 13(2), (1974); Contraception, 7(5), 367-379, (1973); Reproduction, 2(1), 61-62, (1975); International Journal of Fertility, 20, 156-160, (1975)] to test the use of several progestins, among others levonorgestrel, as routine postcoital contraceptives. Routine postcoital contraception means that women, who have non-regular sexual life, use the medicine in a

planned way, but after the coitus. The single daily doses used were between 150 µg and 1000 µg. The results of the studies showed that the postcoital contraceptive efficacy of levonorgestrel – if it is used alone – was low even in 1 mg dose.

A. A. Yuzpe and his coworkers reported in *The Journal of Reproductive Medicine* [13(2), (1974)] the results of those studies where a pharmaceutical composition containing 100 µg of ethinyl-estradiol and 1.0 mg of norgestrel was used as postcoital contraceptive in a single dose. The composition was administered within five days of the unprotected coitus. Later the method was modified. On the one hand the period of the possible use of the composition was reduced from 5 days to 72 hours, on the other hand the dose was doubled that way that the administration was repeated 12 hours after the first one. [*Fertility and Sterility*, 28, 932-936, (1977), *ibid.* 37, 508-513 (1982); *International Journal of Gynaecology and Obstetrics*, 15, 133-136, (1977)]. This modification increased the success of the method.

After the studies of A. A. Yuzpe and his co-workers several other trials were carried out to prove the efficacy of this combination. In these studies the total dose of ethinyl-estradiol was 0.2 mg combined with 2.0 mg of norgestrel or 1.0 mg of levonorgestrel. The results of the studies showed that although the above administration (Yuzpe regimen) caused less side-effects than the estrogens used earlier in high doses (mainly in the sixties), the relative incidence of nausea and vomiting was still very high (50 and 20 %, respectively). These side-effects are due to the estrogen effect and they cause the decrease in compliance, moreover, if vomiting occurs, it decreases the efficacy of the treatment.

The use of levonorgestrel in emergency contraception was discovered in the 1990's. The results of the studies were reported in two well-documented publications [*Lancet*, 352, 428-433, (1998) and *Human Reproduction*, 8(3), 389-392, (1993)]. The efficacy of tablets containing only 0.75 mg of levonorgestrel and the combined tablets of Yuzpe method containing 0.1 mg of ethinyl-estradiol + 1.0 mg levonorgestrel were studied by administering the doses 12 hours apart within 48 as well as within 72 hours of unprotected coitus. The results showed that protection with two tablets containing 0.75 mg of levonorgestrel was better than with the Yuzpe regimen, but the women, who received only levonorgestrel, observed less side-effects, which could be due to the lack of ethinyl-estradiol.

The mechanism of action of levonorgestrel used as postcoital contraceptive was investigated in several studies. Keserü and Garmendia showed that the antioviulatory effect probably depends partly on the time elapsed between taking the last tablet and the time of

ovulation, partly on the quantity of the applied hormone [Contraception, 10, (1974)]. According to other authors besides the inhibition of ovulation other factors can also influence the contraceptive effect [Contraception, 63, 123-129, (2001)]. Levonorgestrel administered in the follicular phase decreased the proliferation activity of the endometrium, while in the luteal phase there was no effect [Contraception, 39(3), 275-289, (1989)].

Several trials were conducted to show the effect of levonorgestrel on the cervical mucus, which could be observed a few hours after the administration. Levonorgestrel inhibits the sperms getting into the upper genital tract in such a way that it causes the thickening of the cervical mucus almost immediately after the absorption of the hormone. It was also shown that after the administration of 400 µg of levonorgestrel the alkalization of the intrauterine fluid starts already after 4 hours of administration and it lasts for approximately 48 hours. This effect can play a role in the inhibition of the movement of sperms, consequently in the contraceptive effect as well [Contraception, 11(1), (1975)].

The studies showed that two pharmaceutical compositions containing 0.75-0.75 mg of levonorgestrel used at 12 hours' interval within 72 hours after the unprotected coitus successfully inhibited the conceptions which otherwise might have occurred. The efficacy was significantly better than the efficacy of the Yuzpe regimen used worldwide earlier. Because of the lack of the estrogen component, side effects (nausea, feeling of sickness, vomiting) leading to the decrease in compliance and the efficacy of the treatment were observed far less frequently. The results of the clinical studies showed that the efficacy was the better the earlier the treatment started after the coitus. However, according to experience, if women wanted to follow the instructions correctly, they often delayed taking the first tablet so as taking the second dose after 12 hours would not fall on an extremely inconvenient time (for example 3 o'clock in the morning). The results of the studies showed that the prescription of 12 hours' interval between the two doses decreased the compliance. According to statistical data the majority of women took the second dose within 12 to 16 hours after the first one [Lancet, 352, 428-433, (1998)].

The results of the study of the mechanism of action of levonorgestrel used as postcoital contraceptive showed that the anti-ovulatory effect had great importance. According to the literature [Contraception, 63, 123-129, (2001)] the anti-ovulatory effect is appr. 42 % of the total effect, while the rest is distributed among the effects on the cervical mucus, the migration of sperms, zygote transport through the fallopian tube, the endometrium and the implantation.

The anti-ovulatory effect depends partly on the quantity of the applied hormone, partly on the time elapsed between the administration and the expected time of ovulation. This seems to support the importance of the 12-hour interval.

According to the above mentioned facts, taking 0.75 mg of levonorgestrel for emergency contraception twice at 12-hour interval within 72 hours of the coitus seemed to be reasonable. Despite of this we studied the possibility of applying the two doses at the same time within 72 hours of the unprotected coitus so as to eliminate the disadvantages of the 12-hour interval. Surprisingly it was found that the administration of two doses of 0.75 mg of levonorgestrel as an active ingredient at the same time did not cause a decrease in efficacy.

Therefore the object of this invention is a dosage regimen for emergency contraception and a pharmaceutical composition for the application of this regimen. The regimen according to this invention is that a single dose containing only 1.5 ± 0.2 mg of levonorgestrel as active ingredient is administered to women to be treated with a pharmaceutical composition within 72 hours of unprotected coitus. Further objects of this invention are the dosage units required to carry out the above regimen.

The dosage units required to carry out the above regimen can be in solid or liquid state, and they can be for example tablets, film-coated tablets, coated tablets, capsules, pills or powder preparations. The lyophilized powder ampoule preparations - making the in situ preparation of liquid compositions possible - also belong to them. Liquid compositions can be for example solutions for injection or infusion.

The efficacy of the regimen according to this invention was compared with the known regimen administering 0.75-0.75 mg of levonorgestrel 12 hours apart in the following trials.

In a double-blind, randomized, multicentre, multinational trial 1,356 women received 0.75-0.75 mg of levonorgestrel at 12-hour interval in the traditional way, while 1,356 received in a single dose 1.5 ± 0.2 mg of levonorgestrel within 72 hours of the unprotected coitus. In the group treated in the traditional way the conception rate was 1.77 %, while in the other group treated with a single dose it was 1.47 %. The so-called "Prevented fraction" (this number shows how many percent of the conception which otherwise might happen is prevented by the treatment) was 77.3 % in the group treated in the traditional way, while in the other it was 81.9 %. These data support the advantage of the single dose treatment, although statistical significance can not be proven. The results of the trial proved that the conceptions which

otherwise might have happened could be prevented by a single tablet containing twice 0.75 mg of levonorgestrel at least as effectively as by the known therapy.

During the evaluation of undesired effects it was found that the incidence of nausea was 14.5 % in the traditional group, while in the group treated with a single dose it was 13.7 %. The incidence of vomiting was 1.4 % in both groups. As the new regimen also has the advantageous properties resulting from the lack of the estrogen component, the incidence of nausea, feeling of sickness, vomiting was apparently low. The incidence of other side-effects (diarrhoea, fatigue, dizziness, headache, breast tenderness, lower abdominal pain) was also not differing significantly.

The incidence of menstrual disorders was not increased either by the single administration of 1.5 mg dose of levonorgestrel compared to the administration of two 0.75 mg doses. The incidence of menstrual disorders was 30.9 % in both groups.

The results of the comparative study show that a single dose of 1.5 ± 0.2 mg of levonorgestrel surprisingly prevented the conception which otherwise might have occurred with the same success as if this amount of active ingredient were administered twice at 12-hour interval within 72 hours of the unprotected coitus. However, the single administration increases the compliance and decreases the possibility of incorrect use by women. Regarding side-effects it has the same advantageous properties as the known double dosed composition containing only levonorgestrel for emergency contraception.

The invention is illustrated by the following not limiting Examples:

Example 1

Tablets of 100 mg total weight are prepared from the following ingredients for each tablet:

	levonorgestrel	1.5 mg
5	hydrophilic colloidal silicium dioxide	0.5 mg
	maize-starch	23.5 mg
	potato-starch	0.5 mg
	talcum	2.5 mg
	magnesium stearate	1.0 mg
10	lactose monohydrate	70.5 mg

The tablets of the above composition are prepared by homogenization of the calculated quantity of the active ingredient into the powder mixture of lactose monohydrate and maize-starch, or spraying the solution of it in alcohol and/or in a mixture of alcohol : chloroform onto the above powder mixture of lactose and maize-starch (forming the inner phase) in a fluidization granulation equipment.

Then the granulating liquid prepared from a part of the maize-starch is sprayed into the mixture and the fluid bed is solidified with streaming air. The granulation takes place parallel with the drying. The obtained grains are reggranulated if necessary, hydrophilic colloidal silicium dioxide, the talcum and the magnesium stearate (forming the outer phase) are admixed, then tablets are pressed from the homogenous mixture.

Example 2

Tablets of 100 mg total weight are prepared from the following ingredients for each tablet:

	levonorgestrel	1.5 mg
25	hydrophilic colloidal silicium dioxide	0.5 mg
	talcum	0.5 mg
	magnesium stearate	1.0 mg
	polivinyI-pirrolidon (Polivinodum K-30)	2.5 mg
	croscarmellose sodium	4.0 mg
30	lactose monohydrate	40.0 mg
	microcrystalline cellulose	50.0 mg

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The tablets of the above given composition are prepared by homogenization of the calculated quantity of the active ingredient into the powder mixture of lactose monohydrate and microcrystalline cellulose, or spraying the solution of it in alcohol and/or in a mixture of alcohol : chloroform onto the above powder mixture of lactose and microcrystalline cellulose
5 (forming the inner phase) in a kneading granulation equipment.

Then the granulating liquid prepared from PVP-K30 is added and the product is granulated by kneading. The wet granulates are regranulated, and dried in a microwave vacuum dryer or in a fluidization equipment. Croscarmellose sodium, hydrophilic colloidal silicium dioxide, talcum and magnesium stearate (forming in the outer phase) are mixed to the above
10 granulates, then 100 mg tablets are pressed from the homogenous mixture.

Example 3

Tablets of 100 mg total weight are prepared from the following ingredients for each tablet:

	levonorgestrel	1.5 mg
15	microcrystalline cellulose	50.0 mg
	hydrophilic colloidal silicium dioxide	0.5 mg
	pregelatinized starch	4.0 mg
	ultra amolipectine	3.0 mg
	magnesium stearate	1.0 mg
20	lactose monohydrate	40.0 mg

The above composition of powder mixture is homogenized with the exception of magnesium stearate in a tank or in a container homogenizer, then magnesium stearate is added and the powder mixture is end-homogenized. Then 100 mg tablets are pressed from the homogenous powder mixture.

What we claim is:

1. Pharmaceutical composition for emergency contraception containing levonorgestrel as active ingredient, characterised by containing only 1.5 ± 0.2 mg of levonorgestrel as active ingredient in each application dose in admixture with known excipients, diluents, flavoring or aromatizing, stabilizers, as well as formulation-promoting or formulation-providing additives, commonly used in the pharmaceutical practice.

2. Dosage regimen for emergency contraception using levonorgestrel as active ingredient, characterised by administering a single application dose containing 1.5 ± 0.2 mg of levonorgestrel as active ingredient up to 72 hours of the coitus.

3. Pharmaceutical composition for emergency contraception used according to the dosage regimen described in claim 2 containing levonorgestrel as active ingredient, characterised by containing only 1.5 ± 0.2 mg of levonorgestrel as active ingredient in each application dose in admixture with known excipients, diluents, flavoring or aromatizing, stabilizers, as well as formulation-promoting or formulation-providing additives, commonly used in the pharmaceutical practice.

4. Use of levonorgestrel for the preparation of single application dose pharmaceutical composition for emergency contraception, characterised by containing only 1.5 ± 0.2 mg of levonorgestrel as active ingredient in each application dose in admixture with known excipients, diluents, flavoring or aromatizing, stabilizers, as well as formulation-promoting or formulation-providing additives, commonly used in the pharmaceutical practice.

5. Process for the preparation of single application dose pharmaceutical composition for emergency contraception, characterised by containing only 1.5 ± 0.2 mg of levonorgestrel as active ingredient in each application dose in admixture with known excipients, diluents, flavoring or aromatizing, stabilizers, as well as formulation-promoting or formulation-providing additives, commonly used in the pharmaceutical practice.

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

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	OF FERTILITY REGULATION T F O P M: "Randomised controlled trial of levonorgestrel versus the Yuzpe regimen of combined oral contraceptives for emergency contraception" LANCET, XX, XX, vol. 352, no. 9126, 8 August 1998 (1998-08-08), pages 428-433, XP004265510 ISSN: 0140-6736 See "Protocol" --- -/--	1-5

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

☐ Patent family members are listed in annex.

* Special categories of cited documents:

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INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
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X,P	VON HERTZEN H ET AL: "Low dose mifepristone and two regimens of levonorgestrel for emergency contraception: a WHO multicentre randomised trial" LANCET, XX, XX, vol. 360, no. 9348, 7 December 2002 (2002-12-07), pages 1803-1810, XP004397554 ISSN: 0140-6736 See "Methods" and "Discussion" -----	1-5

RÉGIMEN DE DOSIFICACIÓN Y COMPOSICIÓN FARMACÉUTICA PARA ANTICONCEPCIÓN DE EMERGENCIA

5 Esta invención se refiere a un régimen de dosificación para anticoncepción de emergencia, a composiciones farmacéuticas para el mismo objetivo, al uso de levonorgestrel para la producción de composiciones farmacéuticas para el mismo objetivo, y al proceso de producción de dichas composiciones farmacéuticas.

10 Es sabido que el coito tiene lugar en muchos casos en los que la concepción se ha de evitar por todos los medios. Existen diversos dispositivos y composiciones farmacéuticas disponibles para la prevención de una concepción no deseada en caso de un coito regular y planificado, por ejemplo el condón, el pesario y dispositivos Intrauterinos, así como los diferentes
15 anticonceptivos orales monofásicos o multifásicos.

Pero en el caso de un coito no planificado o un coito con una anticoncepción imperfecta, estos dispositivos no están disponibles o sólo lo están de un modo inadecuado, por lo que después del coito se han de tomar precauciones para
20 evitar la concepción. Esto ocurre por ejemplo en caso de mujeres que no tienen una vida sexual regular o son víctimas de violaciones, o si el dispositivo para evitar la concepción, por ejemplo el condón, se rompe o rasga. Dado que en estos casos la anticoncepción se ha de lograr antes de la implantación del óvulo fecundado - un tiempo relativamente corto -, estos métodos se
25 denominan anticoncepción de emergencia.

El norgestrel y el levonorgestrel, es decir, el isómero D de norgestrel [$\pm 17\alpha$ -13-etil-17-hidroxi-18,19-dinorpregn-4-en-20-in-3-ona], se han utilizado durante mucho tiempo como anticonceptivos en preparados combinados, por ejemplo
30 una composición farmacéutica denominada OVRAL, que apareció en 1968 y contenía 0,05 mg de etnil-estradiol y 0,5 mg de norgestrel. La patente británica nº 1,041,280 describe la preparación de tabletas, cápsulas y suspensiones de actividad anabólica que contenían 5 mg de norgestrel como principio activo, aunque en la descripción de la actividad biológica del principio activo se dice
35 que la actividad antagonista de estrógeno es 53,7 veces mayor que la de la progesterona y la actividad de progestógeno es igual a la de la progesterona.

En la década de 1970 se llevaron a cabo amplios estudios [The Journal of Reproductive Medicine, 13(2), (1974); Contraception, 7(5), 367-379, (1973); Reproduction, 2(1), 61-62, (1975); International Journal of Fertility, 20, 156-160, (1975)] para analizar el uso de diversas progestinas, entre otras el levonorgestrel, como anticonceptivos poscoitales rutinarios. La anticoncepción poscoital rutinaria significa que mujeres que no tienen una vida sexual regular utilizan la medicina de forma planificada, pero después del coito. Las dosis diarias únicas oscilaban entre 150 µg y 1.000 µg. Los resultados de los estudios mostraron que la eficacia anticonceptiva poscoital del levonorgestrel - si se utiliza solo - era baja incluso con dosis de 1 mg.

A. A. Yuzpe y sus colaboradores presentaron en The Journal of Reproductive Medicine [13(2), (1974)] los resultados de dichos estudios en los que se utilizó una composición que contenía 100 µg de etinil-estradiol y 1,0 mg de norgestrel como anticonceptivo poscoital en una dosis única. La composición se administraba en un plazo de cinco días a partir del coito sin protección. Este método se modificó posteriormente. Por una parte, el período de uso posible de la composición se redujo de 5 días a 72 horas y, por otra, la dosis se dobló de modo que la administración se repitió 12 horas después de la primera [Fertility and Sterility, 28, 932-936, (1977), *ibid.* 37, 508-513 (1982); International Journal of Gynaecology and Obstetrics, 15, 133-136, (1977)]. Esta modificación aumentó el éxito del método.

Después de los estudios de A. A. Yuzpe y sus colaboradores se llevaron a cabo otras pruebas diversas para demostrar la eficacia de esta combinación. En estos estudios, la dosis total de etinil-estradiol era de 0,2 mg combinados con 2,0 mg de norgestrel o 1,0 mg de levonorgestrel. Los resultados de estos estudios mostraron que aunque la administración arriba indicada (régimen de Yuzpe) provocaba menos efectos secundarios que los estrógenos anteriormente utilizados en dosis altas (principalmente en los años sesenta), la incidencia relativa de náuseas y vómitos seguía siendo muy alta (50 y 20 %, respectivamente). Estos efectos secundarios se deben al efecto de los estrógenos y provocan una reducción del cumplimiento del tratamiento. Además, si se producen vómitos, reducen la eficacia del tratamiento.

El uso de levonorgestrel en la anticoncepción de emergencia se descubrió en la década de 1990. Los resultados de los estudios se presentaron en dos

publicaciones bien documentadas [Lancet, 352, 428-433, (1998) y Human Reproduction, 8(3), 389-392, (1993)]. La eficacia de tabletas que contenían únicamente 0,75 mg de levonorgestrel y las tabletas combinadas del método de Yuzpe que contenían 0,1 mg de etinil-estradiol + 1,0 mg de levonorgestrel se estudió mediante la administración de las dosis con un intervalo de 12 horas entre ellas tanto en un plazo de 48 horas como en un plazo de 72 horas a partir del coito sin protección. Los resultados mostraron que la protección lograda con dos tabletas que contenían 0,75 mg de levonorgestrel era mejor que con el régimen de Yuzpe, pero las mujeres que sólo recibieron levonorgestrel presentaban menos efectos secundarios, lo que podría deberse a la falta de etinil-estradiol.

El mecanismo de acción del levonorgestrel utilizado como anticonceptivo poscoital se investigó en varios estudios. Keresü y Garmendica demostraron que el efecto antioulatorio probablemente depende en parte del tiempo transcurrido entre la toma de la última tableta y el momento de la ovulación y en parte de la cantidad de la hormona administrada [Contraception, 10, (1974)]. De acuerdo con otros autores, en el efecto anticonceptivo también pueden influir otros factores además de la inhibición de la ovulación [Contraception, 63, 123-129, (2001)]. El levonorgestrel administrado en la fase folicular redujo la actividad de proliferación del endometrio, mientras que en la fase luteínica no produjo ningún efecto [Contraception, 39(3), 275-289, (1989)].

Se llevaron a cabo varias pruebas para demostrar el efecto del levonorgestrel en el moco cervical, que se pudo observar unas horas después de la administración. El levonorgestrel impide que el esperma llegue al tracto genital superior provocando el engrosamiento del moco cervical casi inmediatamente después de la absorción de la hormona. También se demostró que después de la administración de 400 µg de levonorgestrel, la alcalinización del flujo intrauterino comienza tan solo 4 horas después de la administración y dura aproximadamente 48 horas. Este efecto puede contribuir a la inhibición del movimiento del esperma y, por consiguiente, también al efecto anticonceptivo [Contraception, 11(1), (1975)].

Los estudios demostraron que dos composiciones farmacéuticas que contenían 0,75-0,75 mg de levonorgestrel utilizadas con un intervalo de 12 horas en un plazo de 72 horas después del coito sin protección inhibieron con

éxito las concepciones que se podrían haber producido en otro caso. La eficacia era considerablemente mejor que la eficacia del régimen de Yuzpe anteriormente utilizado en todo el mundo. Debido a la falta del componente de estrógeno, los efectos secundarios (náusea, sensación de malestar, vómitos) que conducen a una reducción del cumplimiento del tratamiento y de la eficacia del mismo se observaron con mucha menos frecuencia. Los resultados de los estudios clínicos mostraron que la eficacia era mejor cuanto antes comenzara el tratamiento después del coito. Sin embargo, de acuerdo con la experiencia adquirida, si las mujeres deseaban seguir las instrucciones correctamente, con frecuencia retrasaban la toma de la primera tableta para que la toma de la segunda tableta 12 horas después no cayera a una hora extremadamente inoportuna (por ejemplo las 3 en punto de la mañana). Los resultados de los estudios demostraron que la prescripción de las 12 horas de intervalo entre las dos dosis reducía el cumplimiento del tratamiento. De acuerdo con los datos estadísticos, la mayoría de las mujeres tomó la segunda dosis en un plazo entre 12 y 16 horas después de la primera [Lancet, 352, 428-433, (1998)].

Los resultados del estudio del mecanismo de acción del levonorgestrel utilizado con anticonceptivo poscoital mostraron que el efecto antiovulatorio tenía una gran importancia. De acuerdo con la literatura [Contraception, 63, 123-129, (2001)], el efecto antiovulatorio representa aproximadamente un 42 % del efecto total, mientras que el resto se distribuye entre los efectos en el moco cervical, la migración de espermatozoides, el transporte del cigoto a través de la trompa de Falopio, el endometrio y la implantación. El efecto antiovulatorio depende en parte de la cantidad de la hormona administrada y en parte del tiempo transcurrido entre la administración y el tiempo de ovulación previsto. Esto parece apoyar la importancia del intervalo de 12 horas.

De acuerdo con los hechos arriba mencionados, la toma de 0,75 mg de levonorgestrel para anticoncepción de emergencia dos veces con un intervalo de 12 horas en un plazo de 72 horas a partir del coito parecía razonable. A pesar de ello, estudiamos la posibilidad de administrar las dos dosis al mismo tiempo en un plazo de 72 horas a partir del coito sin protección, para eliminar así las desventajas del intervalo de 12 horas. Sorprendentemente se comprobó que la administración simultánea de dos dosis de 0,75 mg de levonorgestrel como principio activo no provocaba una reducción de la eficacia.

Por consiguiente, el objeto de esta invención consiste en un régimen de dosificación para anticoncepción de emergencia y una composición farmacéutica para la administración de este régimen. El régimen de acuerdo con esta invención consiste en administrar una dosis única que contiene sólo

5 1,5 ± 0,2 mg de levonorgestrel como principio activo a mujeres que deban ser tratadas con una composición farmacéutica en un plazo de 72 horas después de un coito sin protección. Otros objetos de esta invención consisten en las unidades de dosificación necesarias para llevar a cabo el régimen arriba indicado.

10

Las unidades de dosificación necesarias para llevar a cabo el régimen arriba indicado se pueden encontrar en estado sólido o líquido, y pueden consistir por ejemplo en tabletas, tabletas revestidas con una película, tabletas revestidas, cápsulas, píldoras o preparados en polvo. También entran en consideración los

15 preparados en ampolla de polvo liofilizado, que posibilitan la preparación *in situ* de composiciones líquidas. Las composiciones líquidas pueden ser por ejemplo soluciones para inyección o infusión. La eficacia del régimen de acuerdo con esta invención se comparó con el régimen conocido consistente en la administración de 0,75-0,75 mg de levonorgestrel con un intervalo de 12 horas

20 en los ensayos descritos a continuación.

En un ensayo doble ciego, aleatorio, multicentro y multinacional, 1.356 mujeres recibieron 0,75-0,75 mg de levonorgestrel con un intervalo de 12 horas del modo tradicional, mientras que otras 1.356 mujeres recibieron una dosis única

25 de 1,5 ± 0,2 mg de levonorgestrel en un plazo de 72 horas a partir del coito sin protección. En el grupo tratado del modo tradicional, la proporción de concepciones fue de un 1,77 %, mientras que en el otro grupo, tratado con una dosis única, la proporción fue de un 1,47 %. La, así llamada, "fracción prevenida" (esta cifra muestra qué porcentaje de las concepciones que se

30 podrían haber producido en otro caso es prevenido por el tratamiento) era de un 77,3 % en el grupo tratado del modo tradicional, mientras que en el otro grupo era de un 81,9 %. Estos datos apoyan las ventajas del tratamiento de dosis única, aunque no se puede demostrar una importancia estadística. Los resultados del ensayo demostraron que las concepciones que se podrían haber

35 producido en otro caso se pudieron prevenir mediante una sola tableta que contenía dos veces 0,75 mg de levonorgestrel como mínimo con la misma eficacia que mediante la terapia conocida.

Durante la evaluación de los efectos no deseados se comprobó que la
 incidencia de náuseas era de un 14,5 % en el grupo tradicional, mientras que
 en el grupo tratado con una dosis única era de un 13,7 %. La incidencia de
 5 vómitos era de un 1,4 % en los dos grupos. Dado que el nuevo régimen
 también tiene las propiedades ventajosas resultantes de la falta de
 componente de estrógeno, la incidencia de náuseas, sensación de malestar y
 vómitos era aparentemente baja. La incidencia de otros efectos secundarios
 10 (diarrea, cansancio, mareo, dolor de cabeza, sensibilidad de pecho, dolor
 hipogástrico) tampoco difería de forma significativa. La incidencia de trastornos
 menstruales tampoco aumentó por la administración única de la dosis de 1,5
 mg de levonorgestrel en comparación con la administración de dos dosis de
 0,75 mg. La incidencia de trastornos menstruales era de un 30,9 % en los dos
 grupos.

15 Los resultados del estudio comparativo muestran que una dosis única de $1,5 \pm$
 0,2 mg de levonorgestrel sorprendentemente previno la concepción que podría
 haberse producido en otro caso con el mismo éxito que si dicha cantidad de
 principio activo se hubiera administrado en dos veces con un intervalo de 12
 20 horas en un plazo de 72 horas a partir del coito sin protección. Sin embargo, la
 administración única aumenta el cumplimiento del tratamiento y reduce la
 posibilidad de un uso incorrecto por parte de las mujeres. En lo que respecta a
 los efectos secundarios, tiene las mismas propiedades ventajosas que la
 composición de dos dosis conocida que contiene únicamente levonorgestrel
 25 para anticoncepción de emergencia.

La invención se ilustra mediante los siguientes ejemplos no limitativos:

Ejemplo 1

30 Se preparan tabletas con un peso total de 100 mg a partir de los siguientes
 ingredientes para cada tableta:

	Levonorgestrel		1,5 mg
35	Dióxido de silicio coloidal hidrófilo	0,5 mg	
	Almidón de maíz		23,5 mg
	Fécula de patata		0,5 mg

Talco	2,5 mg
Estearato de magnesio	1,0 mg
Monohidrato de lactosa	70,5 mg

5 Las tabletas con la composición arriba indicada se preparan mediante
homogeneización de la cantidad calculada del principio activo en la mezcla en
polvo de monohidrato de lactosa y almidón de maíz, o mediante pulverización
de la solución de la misma en alcohol y/o en una mezcla de alcohol /
cloroformo sobre la mezcla en polvo de lactosa y almidón de maíz arriba
10 indicada (que forma la fase interna) en un equipo de granulación por
fluidización.

Después, el líquido de granulación preparado con una parte del almidón de
maíz se pulveriza en la mezcla y el lecho fluidizado se solidifica con una
15 corriente de aire. La granulación tiene lugar paralelamente con el secado. Los
granos obtenidos se regranulan en caso necesario, se incorporan el dióxido de
silicio coloidal hidrófilo, el talco y el estearato de magnesio (que forman la fase
externa), y después se prensan las tabletas a partir de la mezcla homogénea.

20

Ejemplo 2

Se preparan tabletas con un peso total de 100 mg a partir de los siguientes
25 ingredientes para cada tableta:

	Levonorgestrel	1,5 mg
	Dióxido de silicio coloidal hidrófilo	0,5 mg
	Talco	0,5 mg
30	Estearato de magnesio	1,0 mg
	Polivinil-pirrolidona (Polivinodum K-30)	2,5 mg
	Croscarmelosa de sodio	4,0 mg
	Monohidrato de lactosa	40,0 mg
	Celulosa microcristalina	50,0 mg

35

Las tabletas con la composición arriba indicada se preparan mediante
homogeneización de la cantidad calculada del principio activo en la mezcla en

polvo de monohidrato de lactosa y celulosa microcristalina, o mediante pulverización de la solución de la misma en alcohol y/o en una mezcla de alcohol / cloroformo sobre la mezcla en polvo de lactosa y celulosa microcristalina arriba indicada (que forma la fase interna) en un equipo de granulación por amasamiento.

Después se añade el líquido de granulación preparado de PVP-K30 y el producto se granula por amasamiento. Los granulados húmedos se regranulan y se secan en un secador de vacío por microondas o en un equipo de fluidización. La croscarmelosa de sodio, el dióxido de silicio coloidal hidrófilo, el talco y el estearato de magnesio (que forman la fase externa) se mezclan con los granulados arriba indicados y después se prensan tabletas de 100 mg a partir de la mezcla homogénea.

15

20

Ejemplo 3

Se preparan tabletas con un peso total de 100 mg a partir de los siguientes ingredientes para cada tableta:

25	Levonorgestrel	1,5 mg
	Celulosa microcristalina	50,0 mg
	Dióxido de silicio coloidal hidrófilo	0,5 mg
	Almidón pregelatinizado	4,0 mg
	Ultra amilo-pectina	3,0 mg
30	Estearato de magnesio	1,0 mg
	Monohidrato de lactosa	40,0 mg

La composición arriba indicada de la mezcla en polvo se homogeneiza excepto el estearato de magnesio en un depósito o en un homogeneizador de recipiente, después se añade el estearato de magnesio y la mezcla en polvo se homogeneiza por completo. A continuación se prensan tabletas de 100 mg a partir de la mezcla en polvo homogénea.

35

REIVINDICACIONES

- 1.- Composición farmacéutica para anticoncepción de emergencia que contiene levonorgestrel como principio activo, caracterizada porque
5 contiene únicamente $1,5 \pm 0,2$ mg de levonorgestrel como principio activo en cada dosis de administración mezclados con excipientes conocidos, diluyentes, saborizantes o aromatizantes, estabilizadores, así como aditivos promotores o facilitadores de formulación utilizados normalmente en la práctica farmacéutica.
10
- 2.- Régimen de dosificación para anticoncepción de emergencia utilizando levonorgestrel como principio activo, caracterizado porque se administra una dosis única que contiene $1,5 \pm 0,2$ mg de levonorgestrel como principio activo en un plazo hasta 72 horas a partir del coito.
15
- 3.- Composición farmacéutica para anticoncepción de emergencia utilizada de acuerdo con el régimen de dosificación descrito en la reivindicación 2, que contiene levonorgestrel como principio activo, caracterizada porque contiene únicamente $1,5 \pm 0,2$ mg de levonorgestrel como principio activo en cada dosis de administración mezclados con excipientes conocidos, diluyentes, saborizantes o aromatizantes, estabilizadores, así como aditivos promotores o facilitadores de formulación utilizados normalmente en la práctica farmacéutica.
20
- 25 4.- Utilización de levonorgestrel para la preparación de una composición farmacéutica de dosis de administración única para anticoncepción de emergencia, caracterizada porque contiene únicamente $1,5 \pm 0,2$ mg de levonorgestrel como principio activo en cada dosis de administración mezclados con excipientes conocidos, diluyentes, saborizantes o aromatizantes, estabilizadores, así como aditivos promotores o facilitadores de formulación utilizados normalmente en la práctica farmacéutica.
30
- 35 5.- Proceso para la preparación de una composición farmacéutica de dosis de administración única para anticoncepción de emergencia, caracterizada porque contiene únicamente $1,5 \pm 0,2$ mg de levonorgestrel como principio activo en cada dosis de administración

mezclados con excipientes conocidos, diluyentes, saborizantes o aromatizantes, estabilizadores, así como aditivos promotores o facilitadores de formulación utilizados normalmente en la práctica farmacéutica.

RÉGIMEN DE DOSIFICACIÓN Y COMPOSICIÓN FARMACÉUTICA PARA ANTICONCEPCIÓN DE EMERGENCIA

- 5 **Resumen:** La invención se refiere a un régimen de dosificación para anticoncepción de emergencia, a composiciones farmacéuticas para el mismo objetivo, al uso de levonorgestrel para la producción de composiciones farmacéuticas para el mismo objetivo, y al proceso de producción de dichas composiciones farmacéuticas. De acuerdo con la invención, la anticoncepción
- 10 de emergencia llevada a cabo mediante el uso de levonorgestrel como principio activo se caracteriza por la administración de una dosis única que contiene $1,5 \pm 0,2$ mg de levonorgestrel como principio activo hasta 72 horas después del coito. Las composiciones farmacéuticas para anticoncepción de
- 15 emergencia de acuerdo con la invención contienen únicamente $1,5 \pm 0,2$ mg de levonorgestrel como principio activo en cada dosis de administración mezclados con excipientes conocidos, diluyentes, saborizantes o aromatizantes, estabilizadores, así como aditivos promotores o facilitadores de formulación utilizados normalmente en la práctica farmacéutica.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Article 36 and Rule 70)

37

37

Applicant's or agent's file reference 0105173WOKB	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416)	
International application No. PCT/HU02/00129	International filing date (day/month/year) 26.11.2002	Priority date (day/month/year) 27.11.2001
International Patent Classification (IPC) or both national classification and IPC A61K31/565		
Applicant RICHTER GEDEON VEGYESZETI GYAR RT. et al.		
1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of 4 sheets, including this cover sheet. ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT). These annexes consist of a total of sheets.		
3. This report contains indications relating to the following items: I ☒ Basis of the opinion II ☐ Priority III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV ☐ Lack of unity of invention V ☒ Reasoned statement under Rule 66.2(a)(II) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI ☐ Certain documents cited VII ☐ Certain defects in the international application VIII ☐ Certain observations on the international application		
Date of submission of the demand 16.06.2003	Date of completion of this report 11.08.2003	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80286 Munich Tel. +49 89 23699 - 0 Tlx: 523656 epmu d Fax: +49 89 23699 - 4465	Authorized Officer Cattell, James Telephone No. +49 89 23699-8468 	

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**International application No. **PCT/HU02/00129****I. Basis of the report**

1. With regard to the elements of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, Pages

1-7 as originally filed

Claims, Numbers

1-5 as originally filed

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
☐ the language of publication of the international application (under Rule 48.3(b)).
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
☐ filed together with the international application in computer readable form.
☐ furnished subsequently to this Authority in written form.
☐ furnished subsequently to this Authority in computer readable form.
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/HU02/00129**

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes: Claims	1-7
	No: Claims	
Inventive step (IS)	Yes: Claims	1-7
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-7
	No: Claims	

2. Citations and explanations

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/HU02/00129

V.

- 1). The cited prior art does not disclose the specific dosage of levonorgestrel of the claims (Art 33(2) PCT).
- 2). In the field of contraception is it not obvious to change the dosage of any hormone, in this case double the dosage, with the expectation of success. The claims can therefore be regarded as inventive under Article 33(2) PCT.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 0105173WOKB	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/HU 02/00129	International filing date (day/month/year) 26/11/2002	(Earliest) Priority Date (day/month/year) 27/11/2001
Applicant RICHTER GEDEON VEGYESZETI GYAR RT.		

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 3 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, the international search was carried out on the basis of the sequence listing :



contained in the international application in written form.



filed together with the international application in computer readable form.



furnished subsequently to this Authority in written form.



furnished subsequently to this Authority in computer readable form.



the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.



the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

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:

5. With regard to the abstract,

the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

as suggested by the applicant.



because the applicant failed to suggest a figure.



because this figure better characterizes the invention.



None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/HU 02/00129

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/565

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

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

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

EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	OF FERTILITY REGULATION T F O P M: "Randomised controlled trial of levonorgestrel versus the Yuzpe regimen of combined oral contraceptives for emergency contraception" LANCET, XX, XX, vol. 352, no. 9126, 8 August 1998 (1998-08-08), pages 428-433, XP004265510 ISSN: 0140-6736 See "Protocol" --- -/--	1-5

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

☐ Patent family members are listed in annex.

* 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 document 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.
- *G* document member of the same patent family

Date of the actual completion of the international search

19 February 2003

Date of mailing of the international search report

26/02/2003

Name and mailing address of the ISA

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Authorized officer

Cattell, James

INTERNATIONAL SEARCH REPORT

International Application No
PCT/HU 02/00129

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	VON HERTZEN H ET AL: "Low dose mifepristone and two regimens of levonorgestrel for emergency contraception: a WHO multicentre randomised trial" LANCET, XX, XX, vol. 360, no. 9348, 7 December 2002 (2002-12-07), pages 1803-1810, XP004397554 ISSN: 0140-6736 See "Methods" and "Discussion" -----	1-5

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No. 44

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) 0105173WOKB

Box No. I TITLE OF INVENTION

DOSAGE REGIMEN AND PHARMACEUTICAL COMPOSITION FOR EMERGENCY CONTRACEPTION

Box No. II APPLICANT

☐ This person is also inventor

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

RICHTER GEDEON VEGYÉSZETI GYÁR RT.
H-1103 Budapest
Gyömrői út 19-21.
HUNGARY

Telephone No.
36-1-4314487Facsimile No.
36-1-4326005

Teleprinter No.

Applicant's registration No. with the Office

State (that is, country) of nationality:

HU

State (that is, country) of residence:

HU

This person is applicant
for the purposes of:☐ all designated
States☒ all designated States except
the United States of America☐ the United States
of America only☐ the States indicated in
the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

VAN LOOK, Paul F.A.
avenue Appia 20
1211 Geneva 27
Switzerland

This person is:

☐ applicant only☒ applicant and inventor☐ inventor only (If this check-box
is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

CH

State (that is, country) of residence:

CH

This person is applicant
for the purposes of:☐ all designated
States☐ all designated States except
the United States of America☒ the United States
of America only☐ the States indicated in
the Supplemental Box

Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:

☐ agent☒ common
representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

RICHTER GEDEON VEGYÉSZETI GYÁR RT.
H-1103 Budapest
Gyömrői út 19-21.
HUNGARY

Telephone No.
36-1-4314487Facsimile No.
36-1-4326005

Teleprinter No.

Agent's registration No. with the Office

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

BALOGH, Illésné
H-1222 Budapest
Gárdonyi u. 11.
HUNGARY

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality: HU

State (that is, country) of residence: HU

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

KOMÁNDI, Katalin
H-1111 Budapest
Bertalan Lajos u. 24.
HUNGARY

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality: HU

State (that is, country) of residence: HU

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

NEMES, László
H-1141 Budapest
Bonyhádi u. 98.
HUNGARY

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality: HU

State (that is, country) of residence: HU

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

SZABÓ, Zsolt
H-2141 Csömör
Csalogány u. 33.
HUNGARY

This person is:

- ☐ applicant only
☒ applicant and inventor
☐ inventor only (If this check-box is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality: HU

State (that is, country) of residence: HU

This person is applicant for the purposes of:

- ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Supplemental Box

If the Supplemental Box is not used, this sheet should not be included in the request.

1. If, in any of the Boxes, except Boxes Nos. VIII(i) to (v) for which a special continuation box is provided, the space is insufficient to furnish all the information: in such case, write "Continuation of Box No." (indicate the number of the Box) and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:

Cont. of Box X.

(i) if more than two persons are to be indicated as applicants and/or inventors and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below:

dr. VAN LOOK Paul F.A.

(ii) if, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;

dr. BALOGH Illésné

(iii) if, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;

NEMES László

(iv) if, in addition to the agent(s) indicated in Box No. IV, there are further agents: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;

(v) if, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "patent of addition," or "certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "continuation" or "continuation-in-part": in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;

(vi) if, in Box No. VI, there are more than five earlier applications whose priority is claimed: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI.

2. If, with regard to the precautionary designation statement contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.

dr. SZABÓ Zsolt

Supplemental Box

If the Supplemental Box is not used, this sheet should not be included in the request.

1. If, in any of the Boxes, except Boxes Nos. VIII(i) to (v) for which a special continuation box is provided, the space is insufficient to furnish all the information: in such case, write "Continuation of Box No." (indicate the number of the Box) and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:

(i) if more than two persons are to be indicated as applicants and/or inventors and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;

(ii) if, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;

(iii) if, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;

(iv) if, in addition to the agent(s) indicated in Box No. IV, there are further agents: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;

(v) if, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "patent of addition," or "certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "continuation" or "continuation-in-part": in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;

(vi) if, in Box No. VI, there are more than five earlier applications whose priority is claimed: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI.

2. If, with regard to the precautionary designation statement contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.

Cont. of Box X.

dr. VAN LOOK Paul F.A.
Director, Department of Reproductive
Health and Research
World Health Organization (WHO)*

dr. BALOGH Illésné

dr. KOMÁNDI Katalin

NEMES László

dr. SZABÓ Zsolt

*REMARK: WHO has arranged and funded the clinical trial which lead to the confirmation of the viability of the invention. The exploitation of the invention is by (and subject to the terms of) an agreement with WHO.

Box No. V DESIGNATION OF STATES

Mark the applicable check-boxes below; at least one must be marked.

48

The following designations are hereby made under Rule 4.9(a):

Regional Patent

- ☒ **AP ARIPO Patent:** GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZM Zambia, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT (if other kind of protection or treatment desired, specify on dotted line)
- ☒ **EA Eurasian Patent:** AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ **EP European Patent:** AT Austria, BE Belgium, CH & LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ **OA OAPI Patent:** BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GQ Equatorial Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

National Patent (if other kind of protection or treatment desired, specify on dotted line):

- | | | |
|---|--|--|
| ☒ AE United Arab Emirates | ☒ GM Gambia | ☒ NZ New Zealand |
| ☒ AG Antigua and Barbuda | ☒ HR Croatia | ☒ OM Oman |
| ☒ AL Albania | ☒ HU Hungary | ☒ PH Philippines |
| ☒ AM Armenia | ☒ ID Indonesia | ☒ PL Poland |
| ☒ AT Austria | ☒ IL Israel | ☒ PT Portugal |
| ☒ AU Australia | ☒ IN India | ☒ RO Romania |
| ☒ AZ Azerbaijan | ☒ IS Iceland | ☒ RU Russian Federation |
| ☒ BA Bosnia and Herzegovina | ☒ JP Japan | |
| ☒ BB Barbados | ☒ KE Kenya | ☒ SD Sudan |
| ☒ BG Bulgaria | ☒ KG Kyrgyzstan | ☒ SE Sweden |
| ☒ BR Brazil | ☒ KP Democratic People's Republic of Korea | ☒ SG Singapore |
| ☒ BY Belarus | ☒ KR Republic of Korea | ☒ SI Slovenia |
| ☒ BZ Belize | ☒ KZ Kazakhstan | ☒ SK Slovakia |
| ☒ CA Canada | ☒ LC Saint Lucia | ☒ SL Sierra Leone |
| ☒ CH & LI Switzerland and Liechtenstein | ☒ LK Sri Lanka | ☒ TJ Tajikistan |
| ☒ CN China | ☒ LR Liberia | ☒ TM Turkmenistan |
| ☒ CO Colombia | ☒ LS Lesotho | ☒ TN Tunisia |
| ☒ CR Costa Rica | ☒ LT Lithuania | ☒ TR Turkey |
| ☒ CU Cuba | ☒ LU Luxembourg | ☒ TT Trinidad and Tobago |
| ☒ CZ Czech Republic | ☒ LV Latvia | |
| ☒ DE Germany | ☒ MA Morocco | ☒ TZ United Republic of Tanzania |
| ☒ DK Denmark | ☒ MD Republic of Moldova | ☒ UA Ukraine |
| ☒ DM Dominica | ☒ MG Madagascar | ☒ UG Uganda |
| ☒ DZ Algeria | ☒ MK The former Yugoslav Republic of Macedonia | ☒ US United States of America |
| ☒ EC Ecuador | ☒ MN Mongolia | ☒ UZ Uzbekistan |
| ☒ EE Estonia | ☒ MWMalawi | ☒ VN Viet Nam |
| ☒ ES Spain | ☒ MX Mexico | ☒ YU Yugoslavia |
| ☒ FI Finland | ☒ MZ Mozambique | ☒ ZA South Africa |
| ☒ GB United Kingdom | ☒ NO Norway | ☒ ZM Zambia |
| ☒ GD Grenada | | ☒ ZW Zimbabwe |
| ☒ GE Georgia | | |
| ☒ GH Ghana | | |

Check-boxes below reserved for designating States which have become party to the PCT after issuance of this sheet:

- | | | |
|--------------------------------|--------------------------------|--------------------------------|
| ☐ | ☐ | ☐ |
| ☐ | ☐ | ☐ |

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)

Box No. VI PRIORITY CLAIM

The priority of the following earlier application(s) is hereby claimed:

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country	regional application:* regional Office	international application: receiving Office
item (1) 27 November 2001 (27.11.01)	P01 05173	HU		
item (2)				
item (3)				
item (4)				
item (5)				

☐ Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office) identified above as:

☐ all items ☒ item (1) ☐ item (2) ☐ item (3) ☐ item (4) ☐ item (5) ☐ other, see Supplemental Box

* Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(ii)):

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):

ISA / . . . EPO

Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority):

Date (day/month/year)

Number

Country (or regional Office)

Box No. VIII DECLARATIONS

The following declarations are contained in Boxes Nos. VIII (i) to (v) (mark the applicable check-boxes below and indicate in the right column the number of each type of declaration):

Number of
declarations

- | | | | |
|---|--|---|---|
| ☐ Box No. VIII (i) | Declaration as to the identity of the inventor | : | |
| ☒ Box No. VIII (ii) | Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent | : | 1 |
| ☐ Box No. VIII (iii) | Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application | : | |
| ☐ Box No. VIII (iv) | Declaration of inventorship (only for the purposes of the designation of the United States of America) | : | |
| ☐ Box No. VIII (v) | Declaration as to non-prejudicial disclosures or exceptions to lack of novelty | : | |

Box No. IX CHECK LIST; LANGUAGE OF FILING

This international application contains:		This international application is accompanied by the following item(s) (mark the applicable check-boxes below and indicate in right column the number of each item):		Number of items
(a) the following number of sheets in paper form:		1. ☒ fee calculation sheet		1
request (including declaration sheets)	: 8	2. ☐ original separate power of attorney		:
description (excluding sequence listing part)	: 7	3. ☐ original general power of attorney		:
claims	: 1	4. ☐ copy of general power of attorney; reference number, if any:		:
abstract	: 1	5. ☐ statement explaining lack of signature		:
drawings	:	6. ☐ priority document(s) identified in Box No. VI as item(s):		:
Sub-total number of sheets	: 17	7. ☐ translation of international application into (language):		:
sequence listing part of description (actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (b) below)	:	8. ☐ separate indications concerning deposited microorganism or other biological material		:
Total number of sheets	: 17	9. ☐ sequence listing in computer readable form (indicate also type and number of carriers (diskette, CD-ROM, CD-R or other))		:
(b) sequence listing part of description filed in computer readable form		(i) ☐ copy submitted for the purposes of international search under Rule 13ter only (and not as part of the international application)		:
(i) ☐ only (under Section 801(a)(i))		(ii) ☐ (only where check-box (b)(i) or (b)(ii) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Rule 13ter		:
(ii) ☐ in addition to being filed in paper form (under Section 801(a)(ii))		(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing part mentioned in left column		:
Type and number of carriers (diskette, CD-ROM, CD-R or other) on which the sequence listing part is contained (additional copies to be indicated under item 9(ii), in right column):		10. ☐ other (specify):		:
Figure of the drawings which should accompany the abstract:		Language of filing of the international application: English		

Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

[Signature]
Dr. SZOMBATHELYI Zsolt
Research Director

[Signature]
Dr. POLGAR István
Director
Intellectual Property

For receiving Office use only

1. Date of actual receipt of the purported international application:	2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority (if two or more are competent): ISA /	6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

Box No. VIII (ii) DECLARATION: ENTITLEMENT TO APPLY FOR AND BE GRANTED A PATENT

The declaration must conform to the standardized wording provided for in Section 212; see Notes to Boxes Nos. VIII, VIII (i) to (v) (in general) and the specific Notes to Box No. VIII (ii). If this Box is not used, this sheet should not be included in the request.

Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent (Rules 4.17(ii) and 51bis.1(a)(ii)), in a case where the declaration under Rule 4.17(iv) is not appropriate:

in relation to this international application

RICHTER GEDEON VEGYÉSZETI GYÁR RT. is entitled to apply for and be granted a patent by virtue of the following:

- 1) **RICHTER GEDEON VEGYÉSZETI GYÁR RT.** is entitled as employer of the inventors

**BALOGH Illésné
KOMÁNDI Katalin
NEMES László
SZABÓ Zsolt**

- 2) an assignment from WHO to **RICHTER GEDEON VEGYÉSZETI GYÁR RT.** dated 21 November 2002.

This declaration is made for the purposes of all designations (except the designation of the United States of America)

☐ This declaration is continued on the following sheet, "Continuation of Box No. VIII (ii)".

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

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 se presenta la solicitud.
- Descripción de la invención.
- Dibujos de ser estos pertinentes.
- Comprobante de Pago de las tasas establecidas.

USUARIO RADICADOR

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() ()

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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 o fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.
- Comprobante de pago de las tasas establecidas

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COMPLETA ()

INCOMPLETA () ()

ESQUEMA DE TRAZADO ()

- Indicación de que 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 de trazado
- Comprobante de pago de las tasas establecidas.

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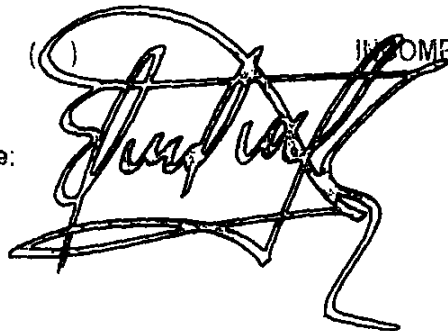
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() ()

COMPLETA ()

INCOMPLETA () ()

Firma Responsable:



Fecha:

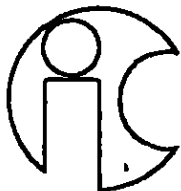
SUPERINDUSTRIA Y COMERCIO

Radicación : 04060435 00000000 Folios: 51

Fecha (MMDD): 2004-06-23 16:16:45

Trámite : 011 DCI-PATENT 379 FASE NACI 011 PRESENTAR

Dependencia: 2029 DIVISION DE NUEVAS CREACIONES



Folio 53

2020
Bogotá DC

Doctor(a)
ALVARO CORREA ORDOÑEZ
Apoderado(a)
RICHTER GEDEON VEGYÉSZETI GYÁN RT.

REFERENCIA:	Radicación No.	04-60435
	Solicitud Internacional	PCT/HU2002/00129
	Fecha inicio fase nacional	27/06/2004
	Trámite	011
	Evento	379
	Actuación	416
	Oficio No.	1351
	Folios	001

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en la Decisión 486 de la Comisión de la Comunidad Andina, el Tratado de Cooperación en Materia de Patentes (PCT), el Reglamento y la Circular Unica de la Superintendencia de Industria y Comercio, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial.

Cúmplase
Dado en Bogotá DC, 23 AGO. 2004


ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones

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