



Industria y Comercio
SUPERINTENDENCIA

SOLICITUD
PATENTE DE INVENCION

PCT

03-47019

21. EXPEDIENTE N°

54. TÍTULO COMPOSICIONES FARMACEUTICAS PARA EL SUMINISTRO ORAL DE AGENTES
FARMACOLOGICAMENTE ACTIVOS.

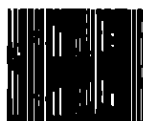
51. CLASIFICACIÓN INTERNACIONAL A 61K 47/00 A61K9/20

71. SOLICITANTE NOVARTIS AG

DOMICILIO BASILEA, SUIZA

74. APODERADO JIMENA ESCOBAR URIBE

22. BOGOTÁ, D. C. JUNIO 4, 2003



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: **NOVARTIS AG**

Dirección: Lichtstrasse 35

Nacionalidad o Domicilio: CH -4056 Basilea,
Suiza.

Lugar de Constitución: Suiza

Teléfono: 41613241111 Fax: 41613227532

E-mail

IDENTIFICACIÓN

C.C. ☐

NIT ☐

C.E. ☐

Otro ☐

Número

3

REPRESENTANTE
O APODERADO
(74)

Nombre: JIMENA ESCOBAR URIBE

Dirección: Cra. 11A No. 94-76 (Of. 305)

Teléfono: 6 162051/61 Fax: 6 161889

E-mail: tm-patent@escobaruribe.com

IDENTIFICACIÓN

C.C. ☒

NIT ☐

C.E. ☐

Otro ☐

Número 39.779.452T.P 68228

4

INVENTOR (ES)
(72)

Nombre: **VER ANEXOS**

Dirección:

Nacionalidad o domicilio:

5

PCT (86)

Solicitud Internacional No. PCT/EP01/14294

Fecha Diciembre 5, 2001

Publicación Internacional No WO 02/45754 A2

Fecha Junio 13, 2002

6 TÍTULO (54) COMPOSICIONES FARMACÉUTICAS PARA EL SUMINISTRO ORAL DE
AGENTES FARMACOLÓGICAMENTE ACTIVOS.

7 Clasificación Internacional (51) A 61K 9/20

8 Prioridad

SI ☒ NO ☐

(33) País de Origen

ESTADOS UNIDOS DE AMÉRICA

(32) Fecha

Diciembre 6, 2000

(31) Número de Solicitud

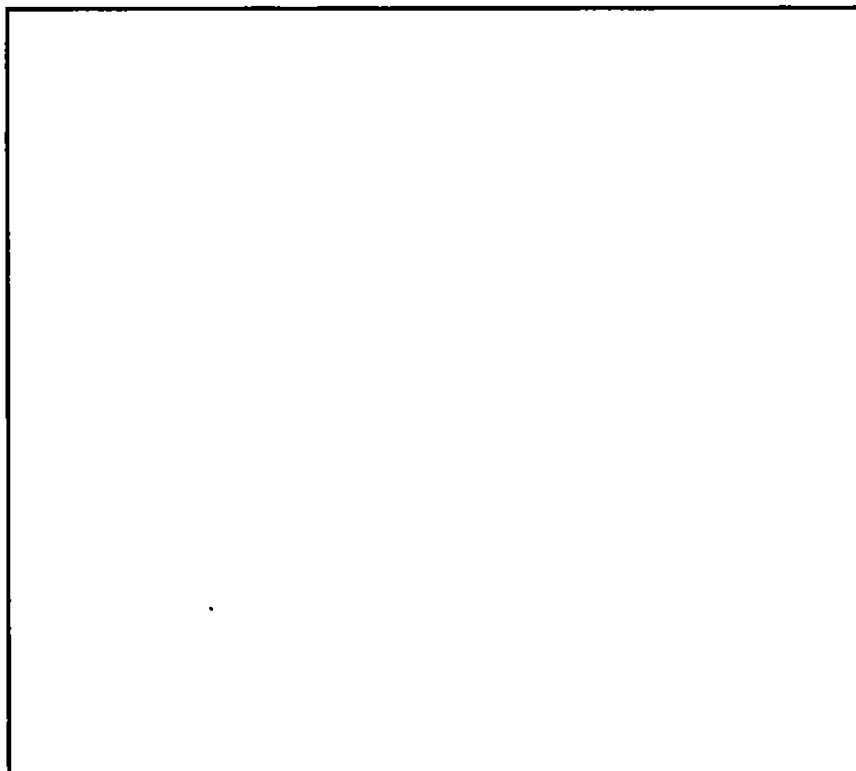
60/251,729

9 Comprobante de pago No. 03 - 30.119

Fecha Abril 30, 2003

- ☒ Comprobante de pago de la tasa de presentación de la solicitud
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica Prot. 17.398
- ☒ Poderes si fuere el caso Protocolo No. 17.398
- ☐ 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 de 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 CARACTERÍSTICA



12 Solicito la concesión de la patente

NOMBRE: JIMENA ESCOBAR URIBE

FIRMA: 

C.C. 39.779.452 DE Usaquén T.P. 68.228

As. 2563/PCT

2583

SUPERINDUSTRIA Y COMERCIO
Radicacion : 03047019 00000000 Folios: 69
Fecha (AMB): 2003-06-04 15:45:41
Tramite : 011 PCT-PATENT 379 FASE NRCI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 03 - 30,119
FECHA : ABRIL 30 DE 2003

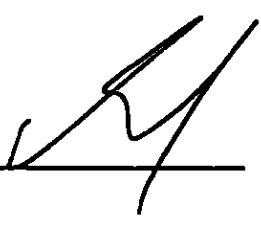
***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
ESCOBAR URIBE ASOCIADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	4885131	30/04/2003	2,000,000.00

***** CONCEPTO *****

CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	400,000.00
	TOTAL :	\$ 400,000.00

SON: CUATROCIENTOS MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

ANEXOS**INVENTORES**

- 1.) **JOSEPH M. AULT**
(Blairstown, New Jersey 07825, Estados Unidos de América);
- 2.) **MOISE AZRIA**
(4054 Basilea, Suiza);
- 3.) **SIMON DAVID BATEMAN**
(Randolph, New Jersey 07869, Estados Unidos de América);
- 4.) **JOSEPH SIKORA**
(Succasunna, New Jersey 07876, Estados Unidos de América);
- 5.) **GREGORY SPARTA**
(Bridgewater, New Jersey 08807, Estados Unidos de América);
- 6.) **REBECCA FAI-YING YANG**
(Randolph, New Jersey 07869, Estados Unidos de América);
- 7.) **JIE XIAO**
(Randolph, New Jersey 07869, Estados Unidos de América).

Solicito expresamente a nombre de la sociedad **NOVARTIS AG.**, sociedad constituida de conformidad con las leyes de Suiza, domiciliada en Lichtstrasse 35, CH -4056 Basilea, Suiza el otorgamiento de Patente para la invención titulada **"COMPOSICIONES FARMACÉUTICAS PARA EL SUMINISTRO ORAL DE AGENTES FARMACOLÓGICAMENTE ACTIVOS"**.

Clase: A 61



JIMENA ESCOBAR URIBE

C.C. 39.779.452 de Usaquen

T.P. 68.228

PATENT COOPERATION TREATY

2563

PC
1
5

From the RECEIVING OFFICE

PCT

To:
BECKER, Konrad
NOVARTIS AG
Corporate Intellectual Property
Patent & Trademark Department
4002 Basel
SUISSE

NOTIFICATION OF THE INTERNATIONAL
APPLICATION NUMBER AND OF THE
INTERNATIONAL FILING DATE

PCT/EP 01/14294
(PCT Rule 20.5(c))

Date of mailing
(day/month/year)

11 03. 2002

Applicant's or agent's file reference
4-31673A ✓

IMPORTANT NOTIFICATION

International application No. ✓
PCT/EP 01/14294 ✓

International filing date (day/month/year) ✓
05/12/2001 ✓

Priority date (day/month/year) ✓
06/12/2000 ✓

Applicant
NOVARTIS AG

Title of the invention

1. The applicant is hereby notified that the international application has been accorded the international application number and the international filing date indicated above.
2. The applicant is further notified that the record copy of the international application was transmitted to the International Bureau on the above date of mailing.

3. ☐ Other: _____

P + TM Dept.

13. März 2002

AGL M/D E/L ES/TS

Kopien:

* The International Bureau monitors the transmittal of the record copy by the receiving Office and will notify the applicant (with Form PCT/IB/301) of its receipt. Should the record copy not have been received by the expiration of 14 months from the priority date, the International Bureau will notify the applicant (Rule 22.1(e)).

Name and mailing address of the Receiving Office
European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040
Fax: (+31-70) 340-3016

Authorized officer

Cocky van Amstel

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. **PCT/EP 01/14294**

(05.12.2001) 05 DEC 2001
International Filing Date

EUROPEAN PATENT OFFICE
PCT INTERNATIONAL APPLICATION
Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) **4-31673A**

Box No. I TITLE OF INVENTION	
Pharmaceutical Compositions for the Oral Delivery of Pharmacologically Active Agents	
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.)	
Novartis AG Lichtstrasse 35 4056 Basel CH	Telephone No. +41 61 324 11 11 Facsimile No. +41 61 322 75 32 Teleprinter No. 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	
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.)	
Novartis-Erfindungen Verwaltungsgesellschaft m.b.H. Brunner Strasse 59 1230 Vienna AT	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: AT	State (that is, country) of residence: AT
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.)	
BECKER, Konrad Novartis AG Corporate Intellectual Property Patent & Trademark Department 4002 Basel CH	Telephone No. +41 61 324 11 11 Facsimile No. +41 61 322 75 32 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.	

Sheet No. ...2...

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)	
<i>If none of the following sub-boxes is used, this sheet should not be included in the request.</i>	
Name and address: <i>(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.)</i> AULT, Joseph M. Four Wards Road Blairstown, NJ 07825 US	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> Applicant's registration No. with the Office
State (that is, country) of nationality: US	State (that is, country) of residence: US
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: <i>(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.)</i> AZRIA, Moise Bundesplatz 6 4054 Basel CH	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> 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	
Name and address: <i>(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.)</i> BATEMAN, Simon David 4 Farrington Lane Randolph, NJ 07869 US	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> Applicant's registration No. with the Office
State (that is, country) of nationality: GB	State (that is, country) of residence: US
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: <i>(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.)</i> SIKORA, Joseph 16 Toby Drive Succasunna, NJ 07876 US	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> Applicant's registration No. with the Office
State (that is, country) of nationality: US	State (that is, country) of residence: US
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.	

Sheet No. ...3...

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)	
<i>If none of the following sub-boxes is used, this sheet should not be included in the request.</i>	
Name and address: <i>(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.)</i> SPARTA, Gregory 66 Claire Drive Bridgewater, NJ 08807 US	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> Applicant's registration No. with the Office
State <i>(that is, country)</i> of nationality: US	State <i>(that is, country)</i> of residence: US
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: <i>(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.)</i> YANG, Rebecca Fal-Ying 7 Hawser Way Randolph, NJ 07869 US	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> Applicant's registration No. with the Office
State <i>(that is, country)</i> of nationality: US	State <i>(that is, country)</i> of residence: US
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: <i>(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.)</i> XIAO, Jie 18 Parkview Road Randolph, NJ 07869 US	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> Applicant's registration No. with the Office
State <i>(that is, country)</i> of nationality: CN	State <i>(that is, country)</i> of residence: US
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: <i>(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.)</i>	This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> Applicant's registration No. with the Office
State <i>(that is, country)</i> of nationality:	State <i>(that is, country)</i> of residence:
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.	

Box No. V DESIGNATION OF STATES

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

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, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT ZM Zambia.
- ☒ 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, 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) GQ Equatorial Guinea.

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

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

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

- ☒ EC Ecuador ☒ OM Oman ☐ ZM Zambia
- ☒ PH Philippines ☒ TN Tunisia (from 10 Dec 01) ☐

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.)

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(1) to (4) 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;*

Continuation of Box No. II
Novartis AG is applicant for all designated States with the exception of: AT (Austria) and US (USA)
 - (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;*

Continuation of Box No. III
Novartis-Erfindungen Verwaltungsgesellschaft m.b.H. is applicant for AT (Austria) only.
 - (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.*

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) 08 December 2000 (08.12.00)	60/251729	US		
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 /		
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	:
☐ 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: (a) the following number of sheets in paper form: request (including declaration sheets) : 7 description (excluding sequence listing part) : 15 claims : 1 abstract : 1 drawings : 0 Sub-total number of sheets : 24 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) : 0 Total number of sheets : 24 (b) sequence listing part of description filed in computer readable form (i) ☐ only (under Section 801(a)(i)) (ii) ☐ in addition to being filed in paper form (under Section 801(a)(ii)) 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):	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): <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 80%;">1. ☒ fee calculation sheet</td> <td style="width: 20%; text-align: right;">1</td> </tr> <tr> <td>2. ☒ original separate power of attorney</td> <td style="text-align: right;">1</td> </tr> <tr> <td>3. ☐ original general power of attorney</td> <td style="text-align: right;"></td> </tr> <tr> <td>4. ☒ copy of general power of attorney; reference number, if any: AV.36671 + 37586</td> <td style="text-align: right;">2</td> </tr> <tr> <td>5. ☐ statement explaining lack of signature</td> <td style="text-align: right;"></td> </tr> <tr> <td>6. ☒ priority document(s) identified in Box No. VI as item(s):</td> <td style="text-align: right;">1</td> </tr> <tr> <td>7. ☐ translation of international application into (language):</td> <td style="text-align: right;"></td> </tr> <tr> <td>8. ☐ separate indications concerning deposited microorganism or other biological material</td> <td style="text-align: right;"></td> </tr> <tr> <td>9. ☐ sequence listing in computer readable form (indicate also type and number of carriers (diskette, CD-ROM, CD-R or other))</td> <td style="text-align: right;"></td> </tr> <tr> <td style="padding-left: 20px;">(i) ☐ copy submitted for the purposes of international search under Rule 13ter only (and not as part of the international application)</td> <td style="text-align: right;"></td> </tr> <tr> <td style="padding-left: 20px;">(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</td> <td style="text-align: right;"></td> </tr> <tr> <td style="padding-left: 20px;">(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing part mentioned in left column</td> <td style="text-align: right;"></td> </tr> <tr> <td>10. ☐ other (specify):</td> <td style="text-align: right;"></td> </tr> </table>	1. ☒ fee calculation sheet	1	2. ☒ original separate power of attorney	1	3. ☐ original general power of attorney		4. ☒ copy of general power of attorney; reference number, if any: AV.36671 + 37586	2	5. ☐ statement explaining lack of signature		6. ☒ priority document(s) identified in Box No. VI as item(s):	1	7. ☐ translation of international application into (language):		8. ☐ separate indications concerning deposited microorganism or other biological material		9. ☐ sequence listing in computer readable form (indicate also type and number of carriers (diskette, CD-ROM, CD-R or other))		(i) ☐ copy submitted for the purposes of international search under Rule 13ter only (and not as part of the international application)		(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		(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing part mentioned in left column		10. ☐ other (specify):	
1. ☒ fee calculation sheet	1																										
2. ☒ original separate power of attorney	1																										
3. ☐ original general power of attorney																											
4. ☒ copy of general power of attorney; reference number, if any: AV.36671 + 37586	2																										
5. ☐ statement explaining lack of signature																											
6. ☒ priority document(s) identified in Box No. VI as item(s):	1																										
7. ☐ translation of international application into (language):																											
8. ☐ separate indications concerning deposited microorganism or other biological material																											
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(i) ☐ copy submitted for the purposes of international search under Rule 13ter only (and not as part of the international application)																											
(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																											
(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing part mentioned in left 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 <i>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).</i>																											
In the name of the applicants The representative H. Becker 03.12.2001 BECKER, Konrad, AV 36671 + 37586																											

For receiving Office use only		
1. Date of actual receipt of the purported international application: (0 5. 12. 01)	05 DEC 2001	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:

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

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
13 June 2002 (13.06.2002)

PCT

(10) International Publication Number
WO 02/45754 A2

(51) International Patent Classification⁷: A61K 47/00

(21) International Application Number: PCT/EP01/14294

(22) International Filing Date: 5 December 2001 (05.12.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/251,729 6 December 2000 (06.12.2000) US

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(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK,
LT, LU, LV, MA, MD, MK, MN, MX, NO, NZ, OM, PH,
PL, PT, RO, RU, SE, SG, SI, SK, TJ, TM, TR, TT, UA, US,
UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): Eurasian patent (AM, AZ,
BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE,
CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC,
NL, PT, SE, TR).

Published:

— without international search report and to be republished
upon receipt of that report

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

(54) Title: PHARMACEUTICAL COMPOSITIONS FOR THE ORAL DELIVERY OF PHARMACOLOGICALLY ACTIVE
AGENTS

(57) Abstract: Solid pharmaceutical compositions suitable for the oral delivery of pharmacologically active agents, e.g. peptides,
comprising a therapeutically-effective amount of a pharmacologically active agent; a crospovidone or povidone; and a delivery agent
for said pharmacologically active agent are disclosed. The compositions provide excellent oral bioavailability of pharmacologically
active agents, particularly calcitonin.



WO 02/45754 A2

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

To:

NOVARTIS AG
Corporate Intellectual Property
Attn. Becker, Konrad
Patent & Trademark Department
CH-4002 Basel
SWITZERLAND

P + TM Dept.

11. Okt. 2002

Date of mailing
(day/month/year)

11/10/2002

Applicant's or agent's file reference

4-31673A

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/EP 01/14294

International filing date
(day/month/year)

05/12/2001

Applicant

NOVARTIS AG

1. ☒ The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 48):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Further action(s): The applicant is reminded of the following:

Shortly after 18 months from the priority date, the International application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the International application, or of the priority claim, must reach the International Bureau as provided in Rules 80bis.1 and 80bis.3, respectively, before the completion of the technical preparations for International publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority

 European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 285(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 16 and 19 cancelled; claims 14, 15 and 18 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 48.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)".

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 4-31673A	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/EP 01/ 14294	International filing date (day/month/year) 05/12/2001	(Earliest) Priority Date (day/month/year) 06/12/2000
Applicant NOVARTIS AG		

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 6 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.

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K9/20 A61K47/34 A61K38/23 A61K35/60 A61P19/08
A61P19/10 A61K47/38 A61K47/18

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 A61P

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, CHEM ABS Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 773 647 A (LEIPOLD HARRY ET AL) 30 June 1998 (1998-06-30) cited in the application column 47, line 47 -column 57, line 52; claims 1-23; examples 1-8 ---	1-14
Y	US 5 866 536 A (HO KOC-KAN ET AL) 2 February 1999 (1999-02-02) cited in the application column 2, line 43 -column 24, line 54; claims 1-23; figures 4,5,7; examples 5-15,34-43,50-58 ---	1-14
X	US 5 002 771 A (DORRELL JAY E ET AL) 26 March 1991 (1991-03-26) ---	1-4,12
Y	column 12, line 34-41; claims 1-7 ---	5,8,10
	--- -/--	



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

"Z" document member of the same patent family

Date of the actual completion of the international search

25 September 2002

Date of mailing of the international search report

11/10/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel (+31-70) 340-2040, Tx 31 651 apo nl,
Fax (+31-70) 340-3016

Authorized officer

Kling, I

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 01/14294

19

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 972 381 A (SANGEKAR SURENDRA A ET AL) 26 October 1999 (1999-10-26)	1
Y	claims 1,2; examples 6,12-20	5
X	WO 00 57857 A (YUHAN CORP) 5 October 2000 (2000-10-05)	1
Y	claims 1-3; examples 1-13	5
X	GB 2 295 966 A (BIOGLAN IRELAND) 19 June 1996 (1996-06-19)	1
Y	claims 1-30	5
P,A	DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; July 2001 (2001-07) LEONE-BAY ANDREA ET AL: "Oral delivery of biologically active parathyroid hormone." Database accession no. PREV200100449260 XP002214663 abstract & PHARMACEUTICAL RESEARCH (NEW YORK), vol. 18, no. 7, July 2001 (2001-07), pages 964-970, ISSN: 0724-8741	1-14

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims 1 and 2 relate to a product defined by reference to a desirable characteristic or property, namely a) a therapeutically effective amount of a pharmacologically active agent
C) a delivery agent

The claims cover all products having these characteristics or properties, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such products. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the products of claims 3 to 10 (i.e. calcitonin and 5-CNAC) e.g. those prepared in examples.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 01/14294

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

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 12 - 14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

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

Remark on Protest

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 01/14294

22

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 5773647	A	30-06-1998	AU 738735 B2	27-09-2001
			AU 6275698 A	26-08-1998
			CA 2319672 A1	13-08-1998
			CA 2319680 A1	13-08-1998
			EP 1093819 A2	25-04-2001
			EP 1015008 A1	05-07-2000
			EP 0993831 A2	19-04-2000
			JP 2001513080 T	28-08-2001
			JP 2001139494 A	22-05-2001
			JP 2001131090 A	15-05-2001
			NZ 337131 A	31-08-2001
			NZ 507275 A	30-11-2001
			NZ 507276 A	01-02-2002
			WO 9834632 A1	13-08-1998
US 5866536	A	02-02-1999	US 5650386 A	22-07-1997
			AU 712222 B2	04-11-1999
			AU 5662996 A	16-10-1996
			BR 9604880 A	19-05-1998
			CA 2214323 A1	03-10-1996
			CN 1190893 A	19-08-1998
			CZ 9703073 A3	18-03-1998
			EP 0817643 A1	14-01-1998
			FI 973828 A	29-09-1997
			HU 9901162 A2	30-08-1999
			JP 2002506418 T	26-02-2002
			NO 974495 A	28-11-1997
			NZ 307319 A	28-10-1999
			PL 322494 A1	02-02-1998
			TR 9701071 T2	22-03-1999
			WO 9630036 A1	03-10-1996
			US 2001023240 A1	20-09-2001
			US 6346242 B1	12-02-2002
			US 5965121 A	12-10-1999
			US 6001347 A	14-12-1999
			US 5989539 A	23-11-1999
			US 6071510 A	06-06-2000
			US 5962710 A	05-10-1999
			AU 2595697 A	22-10-1997
			SI 9720025 A	31-08-1999
			US 2002127202 A1	12-09-2002
			WO 9736480 A1	09-10-1997
			US 6090958 A	18-07-2000
			US 6344213 B1	05-02-2002
			US 6221367 B1	24-04-2001
US 5002771	A	26-03-1991	NONE	
US 5972381	A	26-10-1999	NONE	
WO 0057857	A	05-10-2000	AU 3574500 A	16-10-2000
			WO 0057857 A1	05-10-2000
			US 2002071864 A1	13-06-2002
GB 2295966	A	19-06-1996	IE 950586 A2	01-11-1995
			AT 199495 T	15-03-2001
			AU 4353996 A	03-07-1996
			DE 69520292 D1	12-04-2001

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 01/14294

23

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 2295966	A	DE 69520292 T2	13-06-2001
		DK 800384 T3	17-04-2001
		EP 1057479 A1	06-12-2000
		EP 0800384 A1	15-10-1997
		ES 2154744 T3	16-04-2001
		IE 950946 A1	26-06-1996
		WO 9618386 A1	20-06-1996
		PT 800384 T	29-06-2001
		ZA 9510650 A	09-07-1996

P + TM Dept.

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

20. Nov. 2002

APPL M/D F/L PS/TS

Kopien:

To:

GROS, Florent
Novartis AG
Corporate Intellectual Property
Patent & Trademark Department
4002 Basel
SUISSE

WRITTEN OPINION

(PCT Rule 66)

Date of mailing
(day/month/year)

18/11/2002

No response

appropriate

Applicant's or agent's file reference

4-31673A

REPLY DUE

within 1 / 00 months/days
from the above date of mailing

International application No.

PCT/EP 01/ 14294

International filing date (day/month/year)

05/12/2001

Priority date (day/month/year)

06/12/2000

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

A61K9/20

Applicant

NOVARTIS AG et al.

1. This written opinion is the first drawn up by this International Preliminary Examining Authority.

2. This opinion 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

3. The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4. For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4bis. For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 05/04/2003

Name and mailing address of the IPEA/

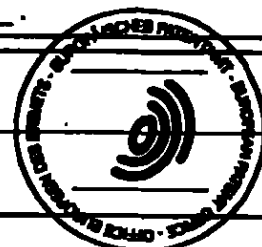


European Patent Office
D-80298 Munich
Tel. (+49-89) 2399-0, Tx: 523656 epmu d
Fax: (+49-89) 2399-4465

Authorized officer

Examiner

Formalities officer
(incl. extension of time limits)
Tel. (+49-89) 2399 2828



I. Basis of the opinion

The basis of this written opinion is the application as originally filed.

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

The question of whether the claimed invention appears to be novel, to involve an inventive step, or to be industrially applicable has not been and will not be the subject of the international preliminary examination in respect of the claims which have not been searched (Article 17(2)(a) or (3) and Rule 66.1(e) PCT; see also international search report).

V. Reasoned statement under Rule 66.2(a)(II) with regard to novelty, inventive step or industrial applicability

1. To the extent that the international preliminary examination has been carried out (see item III above), the following is pointed out:
2. In light of the documents cited in the international search report, it is considered that the invention as defined in at least some of the claims, which have been the subject of an international search report, does not appear to meet the criteria mentioned in Article 33(1) PCT, i.e. does not appear to be novel and/or to involve an inventive step (see international search report, in particular the documents cited X and/or Y and corresponding claim references).
3. If amendments are filed, the applicant should comply with the requirements of Rule 66.8 PCT and indicate the basis of the amendments in the documents of the application as originally filed (Article 34 (2) (b) PCT) otherwise these amendments may not be taken into consideration for the establishment of the international preliminary examination report. The attention of the applicant is drawn to the fact that if the application contains an unnecessary plurality of independent claims, no examination of any of the claims will be carried out.

NB: Should the applicant decide to request detailed substantive examination, then an international preliminary examination report will normally be established directly. Exceptionally the examiner may draw up a second written opinion, should this be explicitly requested.

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ _____

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only	
Identification of IPEA	Date of receipt of DEMAND
Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION	
Applicant's or agent's file reference 4-31673A	
International application No. PCT/EP 01/14294	International filing date (day/month/year) 05 December 2001 (05.12.01)
(Earliest) Priority date (day/month/year) 08 December 2000 (08.12.00)	
Title of invention Pharmaceutical Compositions for the Oral Delivery of Pharmacologically Active Agents	
Box No. II APPLICANT(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.)	
Novartis AG Lichtstrasse 35 4056 Basel CH	
Telephone No. +4161 324 11 11	
Facsimile No. +4161 322 75 32	
Teleprinter No.	
Applicant's registration No. with the Office	
State (that is, country) of nationality: CH	State (that is, country) of residence: CH
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.)	
Novartis-Erfindungen Verwaltungsgesellschaft m.b.H. Brunner Strasse 59 1230 Vienna AT	
State (that is, country) of nationality: AT	State (that is, country) of residence: AT
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.)	
AULT, Joseph M. Four Wards Road Blairstown, NJ 07825 US	
State (that is, country) of nationality: US	State (that is, country) of residence: US
☒ Further applicants are indicated on a continuation sheet.	

Continuation of Box No. II APPLICANT(S)

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

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.)

AZRIA, Molse
Bundesplatz 6
4054 Basel
CH

State (that is, country) of nationality:
CH

State (that is, country) of residence:
CH

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.)

BATEMAN, Simon David
4 Farrington Lane
Randolph, NJ 07869
US

State (that is, country) of nationality:
GB

State (that is, country) of residence:
US

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.)

SIKORA, Joseph
16 Toby Drive
Succasunna, NJ 07876
US

State (that is, country) of nationality:
US

State (that is, country) of residence:
US

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.)

SPARTA, Gregory
66 Claire Drive
Bridgewater, NJ 08807
US

State (that is, country) of nationality:
US

State (that is, country) of residence:
US

☒ Further applicants are indicated on another continuation sheet.

Sheet No. 3.

International application No.
PCT/EP 01/14294

Continuation of Box No. II APPLICANT(S)

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

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.)

YANG, Rebecca Fal-Ying
7 Hawser Way
Randolph, NJ 07869
US

State (that is, country) of nationality:
US

State (that is, country) of residence:
US

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.)

XIAO, Jie
18 Parkview Road
Randolph, NJ 07869
US

State (that is, country) of nationality:
CN

State (that is, country) of residence:
US

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.)

State (that is, country) of nationality:

State (that is, country) of residence:

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.)

State (that is, country) of nationality:

State (that is, country) of residence:

☐ Further applicants are indicated on another continuation sheet.

Sheet No. 4.

International application No.
PCT/EP 01/14284

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

The following person is ☒ agent ☐ common representative
and ☐ has been appointed earlier and represents the applicant(s) also for international preliminary examination.
☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.
☒ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

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.)

GROS, Florent
Novartis AG
Corporate Intellectual Property
Patent & Trademark Department
4002 Basel
CH

Telephone No.
+4161 324 11 11

Facsimile No.
+4161 322 75 32

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.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination to start on the basis of:

- ☒ the international application as originally filed
- the description ☐ as originally filed
☐ as amended under Article 34
- the claims ☐ as originally filed
☐ as amended under Article 19 (together with any accompanying statement)
☐ as amended under Article 34
- the drawings ☐ as originally filed
☐ as amended under Article 34

2. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). (This check-box may be marked only where the time limit under Article 19 has not yet expired.)

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English

- ☒ which is the language in which the international application was filed.
☐ which is the language of a translation furnished for the purposes of international search.
☒ which is the language of publication of the international application.
☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The applicant hereby elects all eligible States (that is, all States which have been designated and which are bound by Chapter II of the PCT)

excluding the following States which the applicant wishes not to elect:

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

- | | | |
|--|---|--------|
| 1. translation of international application | : | sheets |
| 2. amendments under Article 34 | : | sheets |
| 3. copy (or, where required, translation) of amendments under Article 19 | : | sheets |
| 4. copy (or, where required, translation) of statement under Article 19 | : | sheets |
| 5. letter | : | sheets |
| 6. other (specify) | : | sheets |

For International Preliminary
Examining Authority use only

- | received | not received |
|--------------------------|--------------------------|
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |

The demand is also accompanied by the item(s) marked below:

- | | |
|--|---|
| 1. ☒ fee calculation sheet | 5. ☐ statement explaining lack of signature |
| 2. ☐ original separate power of attorney | 6. ☐ sequence listing in computer readable form |
| 3. ☐ original general power of attorney | 7. ☒ other (specify): copy of general sub-authorisation |
| 4. ☐ copy of general power of attorney; reference number, if any: | |

Box No. VII 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 demand).

In the name of the applicants
The representative



14.06.2002

GROS, Florent AV 36671 + 37586

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. ☐ The applicant has been informed accordingly.

4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.

5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

PCT

FEE CALCULATION SHEET

Annex to the Demand

International application No. PCT/EP 01/14294	For International Preliminary Examining Authority use only									
Applicant's or agent's file reference 4-31673A	Date stamp of the IPEA									
Applicant Novartis AG et al.										
CALCULATION OF PRESCRIBED FEES										
1. Preliminary examination fee	EUR 1530.-	☒ P								
2. Handling fee (Applicants from certain States are entitled to a reduction of 75% of the handling fee. Where the applicant is (or all applicants are) so entitled, the amount to be entered at H is 25% of the handling fee.)	EUR 159.-	☒ H								
3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box	EUR 1689.-	TOTAL								
MODE OF PAYMENT										
<table style="width: 100%; border: none;"> <tr> <td style="width: 40%;">☒ authorization to charge deposit account with the IPEA (see below)</td> <td style="width: 60%;">☐ cash</td> </tr> <tr> <td>☐ cheque</td> <td>☐ revenue stamps</td> </tr> <tr> <td>☐ postal money order</td> <td>☐ coupons</td> </tr> <tr> <td>☐ bank draft</td> <td>☐ other (specify):</td> </tr> </table>			☒ authorization to charge deposit account with the IPEA (see below)	☐ cash	☐ cheque	☐ revenue stamps	☐ postal money order	☐ coupons	☐ bank draft	☐ other (specify):
☒ authorization to charge deposit account with the IPEA (see below)	☐ cash									
☐ cheque	☐ revenue stamps									
☐ postal money order	☐ coupons									
☐ bank draft	☐ other (specify):									
AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT <i>(This mode of payment may not be available at all IPEAs)</i>										
<table style="width: 100%; border: none;"> <tr> <td style="width: 50%; vertical-align: top;"> ☒ Authorization to charge the total fees indicated above. ☒ (This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit) Authorization to charge any deficiency or credit any overpayment in the total fees indicated above. </td> <td style="width: 50%; vertical-align: top;"> IPEA/ <u>EP</u> Deposit Account No.: <u>2811 0031</u> Date: <u>14.08.2002</u> Name: <u>Novartis AG</u> Signature: <u>E. Rubelma</u> </td> </tr> </table>			☒ Authorization to charge the total fees indicated above. ☒ (This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit) Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.	IPEA/ <u>EP</u> Deposit Account No.: <u>2811 0031</u> Date: <u>14.08.2002</u> Name: <u>Novartis AG</u> Signature: <u>E. Rubelma</u>						
☒ Authorization to charge the total fees indicated above. ☒ (This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit) Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.	IPEA/ <u>EP</u> Deposit Account No.: <u>2811 0031</u> Date: <u>14.08.2002</u> Name: <u>Novartis AG</u> Signature: <u>E. Rubelma</u>									

TRATADO DE COOPERACION EN MATERIA DE PATENTES

PCT

INFORME EXAMEN PRELIMINAR INTERNACIONAL

(PCT artículo 36 y regla 70)

Referencia del solicitante o agente 4-31673A	PARA PROSEGUIR Ver notificación de la transmisión del examen preliminar Internacional (formato PCT/IPEA/416)	
No. Solicitud Internacional PCT/EP 01/14294	Fecha de presentación internacional (día/mes/año) 05/12/2001	Fecha de prioridad (día/mes/año) 06/12/2000
Clasificación Internacional de Patentes (IPC) o clasificación nacional e IPC A61K9/20		
Solicitante NOVARTIS AG et al.		

1. Este examen preliminar internacional ha sido preparado por esta Autoridad encargada del Examen Preliminar Internacional y es transmitida al solicitante de acuerdo con el artículo 36. 2. Este INFORME consiste de un total de 2 páginas, incluyendo esta hoja. — Este informe también está acompañado por ANEXOS, esto es hojas de la descripción, reivindicaciones y/o dibujos, los cuales han sido modificados y son la base para este Informe y/o hojas que contienen rectificaciones presentadas ante esta Autoridad (ver Regla 70.16 y Sección 607 de las Instrucciones Administrativas bajo el PCT). Estos anexos consisten en un total de ___ hojas.
3. Este informe contiene indicaciones que se relacionan con los siguientes puntos: I. ☒ Base del Informe II. ☐ Prioridad III. ☒ El no-establecimiento de opinión en relación con la novedad, nivel inventivo y aplicación Industrial IV. ☐ Falta de unidad de invención V. ☒ Declaración motivada bajo el Art. 35(2) con relación a la novedad, nivel inventivo o aplicación industrial; citaciones y explicaciones que soportan dicha declaración VI. ☐ Ciertos documentos citados VII. ☐ Ciertos defectos en la solicitud Internacional VIII. ☐ Ciertas observaciones en la solicitud Internacional

Fecha de presentación de la demanda 19/06/2002	Fecha en que se completó este informe 03/01/2003
Nombre y dirección de la autoridad encargada del examen preliminar internacional: Oficina de Patentes Europea D-80298 Munich Tel. +49 89 2399-0 Tx: 523656 epmu d Fax: +49 89 2399 - 4485	Oficial autorizado F RSTER W K Teléfono: +49 89 2399 2828

**INFORME DEL EXAMEN
PRELIMINAR INTERNACIONAL**Solicitud internacional No. PCT/EP 01/14294

I. BASE DEL INFORME

1. La base de este informe del examen preliminar internacional es la solicitud como fue presentada originalmente.

III. El no-establecimiento de opinión en relación con la novedad, nivel inventivo y aplicación industrial

Frente a la pregunta de si la presente invención reivindicada aparenta ser novedosa, si tiene altura inventiva, o es aplicable industrialmente no ha sido objeto del examen preliminar internacional en relación con las reivindicaciones que no han sido buscadas (Art. 17(2) (a) o (3) y Regla 68.1 (a) PCT); ver también el informe de búsqueda internacional).

V. Declaración motivada bajo la Regla 68.2(a)(II) con relación a la novedad, nivel inventivo o aplicación industrial

Si se llevare a cabo el examen preliminar internacional (ver el ítem III mencionado anteriormente), se señala lo siguiente:

A la luz de los documentos citados en el informe de búsqueda internacional, se considera que la invención como es definida en por lo menos algunas de las reivindicaciones, las cuales han sido el objeto del informe de búsqueda internacional, no aparenta cumplir con los criterios mencionados en el Artículo 33 (1) PCT, esto es, no aparenta ser novedosa y/o tener nivel inventivo (ver el informe de búsqueda internacional, en especial los documentos citados X y/o Y, y las referencias citadas).

PATENT COOPERATION TREATY

Corporate Intellectual Property				
13. Jan. 2003 34				
APPL	M/D	F/L	PS	Copy: <i>DE</i>

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

GROS, Florent
Novartis AG
Corporate Intellectual Property
Patent & Trademark Department
4002 Basel
SUISSE

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing (day/month/year) 09/01/2003	
Applicant's or agent's file reference 4-31673A	IMPORTANT NOTIFICATION
International application No. PCT/EP 01/ 14294	International filing date (day/month/year) 05/12/2001
Priority date (day/month/year) 06/12/2000	
Applicant NOVARTIS AG et al.	

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the IPEA/  European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Authorized officer AIMALE MURILLO J Tel. (+49-89) 2399 2828
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Form PCT/IPEA/416 (August 2002) P20473



INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

(Rationalised Report according to the Notice of the President of the EPO published in the OJ11/2001)

Applicant's or agent's file reference...	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
4-31673A		
International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/EP 01/ 14294	05/12/2001	06/12/2000
International Patent Classification (IPC) or national classification and IPC		
A61K9/20		
Applicant		
NOVARTIS AG 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 2 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 consists of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- 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 Article 35(2) 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	Date of completion of this report
19/06/2002	03/01/2003
Name and mailing address of the IPEA/	Authorized officer
 European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	F RSTER W K Tel. (+49-89) 2399 2828

Form PCT/IPEA/409 (cover sheet) P20476 (October 2002)



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No PCT/EP 01/14294

I. Basis of the report

The basis of this international preliminary examination is the application as originally filed.

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

The question of whether the claimed invention appears to be novel, to involve an inventive step, or to be industrially applicable has not been the subject of the international preliminary examination in respect of the claims which have not been searched (Article 17(2)(a) or (3) and Rule 66.1(e) PCT); see also international search report).

V. Reasoned statement under Rule 66.2(a)(II) with regard to novelty, inventive step or industrial applicability

To the extent that the international preliminary examination has been carried out (see item III above), the following is pointed out:

In light of the documents cited in the international search report, it is considered that the invention as defined in at least some of the claims, which have been the subject of an international search report, does not appear to meet the criteria mentioned in Article 33(1) PCT, i.e. does not appear to be novel and/or to involve an inventive step (see international search report, in particular the documents cited X and/or Y and corresponding claim references).

COMPOSICIONES FARMACÉUTICAS PARA EL SUMINISTRO ORAL DE
AGENTES FARMACOLÓGICAMENTE ACTIVOS

Antecedentes de la Invención

5 **1. Campo de la Invención**

La presente invención se refiere a composiciones orales para el suministro de agentes farmacológicamente activos, a métodos para mejorar la biodisponibilidad de agentes farmacológicamente activos oralmente administrados, y
10 a métodos para el tratamiento y/o la prevención de enfermedades en mamíferos, en particular seres humanos, mediante la administración oral de un agente farmacológicamente activo de acuerdo con la invención.

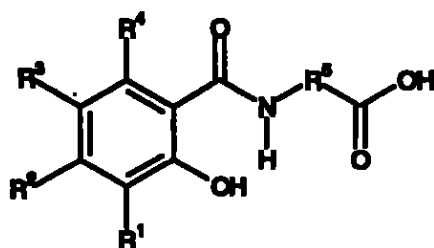
15 **2. Descripción de la Técnica Relacionada**

El suministro oral de agentes farmacológicamente activos es en general la vía de suministro de elección, debido a que es conveniente, relativamente fácil, y generalmente indolora, dando como resultado un mayor
20 cumplimiento del paciente en relación con otros modos de suministro. Sin embargo, las barreras biológicas, químicas, y físicas, tales como el pH variable en el tracto gastrointestinal las poderosas enzimas digestivas, y las membranas gastrointestinales impermeables al agente activo,
25 hacen problemático el suministro oral de algunos agentes

farmacológicamente activos a mamíferos, por ejemplo el suministro oral de calcitoninas, que son hormonas de polipéptidos de cadena larga secretadas por las células parafoliculares de la glándula tiroides en los mamíferos, y
5 por la glándula ultimobranquial de aves y peces, ha probado ser difícil debido, cuando menos en parte, a la estabilidad insuficiente de la calcitonina en el tracto gastrointestinal, así como a la incapacidad de la calcitonina para transportarse fácilmente a través de las paredes intestinales
10 hacia la corriente sanguínea.

Las Patentes de los Estados Unidos de Norteamérica Números 5,773,647 y 5,866,536 describen composiciones para el suministro oral de agentes activos, tales como heparina y calcitonina, con aminoácidos modificados, tales como ácido N-
15 (5-clorosaliciloil)-8-aminocaprílico (5-CNAC), ácido N-(10-[2-hidroxibenzoil]aminodecanoico (SNAD), y ácido N-(8-[2-hidroxibenzoil]amino)caprílico (SNAC). En adición, la Publicación Internacional Número WO 00/059863 da a conocer las sales disódicas de la fórmula I:

20



25

Fórmula I

en donde:

R¹, R², R³, y R⁴ son independientemente hidrógeno, -OH, -NR⁶R⁷, halógeno, alquilo de 1 a 4 átomos de carbono, o alcoxilo de 1 a 4 átomos de carbono;

5 R⁵ es un alquileo de 2 a 16 átomos de carbono sustituido o insustituido, alquencileno de 2 a 16 átomos de carbono sustituido o insustituido, alquilo de 1 a 12 átomos de carbono-(arileno) sustituido o insustituido, o arilo(alquileo de 1 a 12 átomos de carbono) insustituido o
10 insustituido; y

R⁶ y R⁷ son independientemente hidrógeno, oxígeno, o alquilo de 1 a 4 átomos de carbono; e hidratos y solvatos de las mismas, como particularmente eficaces para el suministro oral de agentes activos, tales como calcitonina,
15 ciclosporina, y heparina.

La presente invención describe composiciones farmacéuticas que proporcionan una biodisponibilidad oral todavía mayor de los agentes farmacológicamente activos, por ejemplo péptidos, tales como calcitonina.

20

Compendio de la Invención

De conformidad con lo anterior, la presente invención se refiere a composiciones farmacéuticas que, de una manera muy sorprendente, mejoran mucho la
25 biodisponibilidad oral de los agentes activos, en particular

péptidos. Específicamente, la invención proporciona composiciones farmacéuticas sólidas adecuadas para el suministro oral de agentes farmacológicamente activos, que comprenden:

- 5 1. una cantidad terapéuticamente efectiva de un agente farmacológicamente activo;
2. una crospovidona o povidona; y
3. un agente de suministro para el agente farmacológicamente activo.

10 En otra modalidad, la presente invención proporciona composiciones farmacéuticas sólidas adecuadas para el suministro oral de calcitonina, que comprenden:

1. Una cantidad terapéuticamente efectiva de una calcitonina; y
- 15 2. Una crospovidona o povidona.

 En una modalidad adicional, la invención se refiere a un método para mejorar la biodisponibilidad oral de un agente farmacológicamente activo, comprendiendo este método administrar a un sujeto que necesite dicho agente
20 farmacológicamente activo, una cantidad efectiva de una composición farmacéutica de acuerdo con la presente invención.

 En una modalidad todavía adicional, la invención se refiere a un método de tratamiento de enfermedades
25 relacionadas con los huesos y de desórdenes de calcio, el

cual comprende administrar a un paciente que necesite dicho tratamiento, una cantidad terapéuticamente efectiva de una composición de acuerdo con la presente invención, en donde este agente farmacológicamente activo es calcitonina.

5 Otras características y ventajas de la invención llegarán a quedar más claras a partir de la siguiente descripción detallada de la invención.

Descripción Detallada de la Invención

10 Los agentes farmacológicamente activos adecuados para utilizarse en la presente invención incluyen tanto agentes terapéuticos como preventivos, y se refieren en particular a los agentes que por sí mismos no pasan, o que pasan solamente una pequeña cantidad de la dosis administrada
15 a través de la mucosa gastrointestinal, y/o que son susceptibles a la disociación por los ácidos y las enzimas que se encuentran en el tracto gastrointestinal. Los agentes farmacológicamente activos incluyen, pero no se limitan a, proteínas; polipéptidos; hormonas; polisacáridos incluyendo
20 mezclas de muco-polisacáridos; carbohidratos; lípidos; y combinaciones de los mismos.

 Los ejemplos específicos de los agentes farmacológicamente activos incluyen, pero no se limitan a, los siguientes, incluyendo sus fuentes sintéticas, naturales,
25 o recombinantes: hormona de crecimiento, incluyendo las

hormonas de crecimiento humanas (hGH), hormonas de crecimiento humanas recombinantes (rhGH), hormonas de crecimiento bovinas, y hormonas de crecimiento porcinas; hormonas liberadoras de hormonas de crecimiento; 5 interferones, incluyendo α -, β -, y γ -interferón; interleucina-1; interleucina-2, insulina, incluyendo porcina, bovina, humana, y recombinante humana, que tenga opcionalmente contra-iones, incluyendo sodio, zinc, calcio, y amonio; factor de crecimiento tipo insulina, incluyendo IGF- 10 1; heparina, incluyendo heparina no fraccionada, heparinoides, dermatanos, condroitinas, heparinas de bajo, muy bajo, y ultra-bajo peso molecular; calcitonina, incluyendo de salmón, porcina, de anguila, de pollo, y humana; eritropoyetina; factor natiurético auricular; 15 antígenos; anticuerpos monoclonales, somatostatina; inhibidores de proteasa, adrenocorticotropina, hormona liberadora de gonadotropina; oxitocina, hormona liberadora de hormona leutinizante; hormona estimulante de folículos; glucocerebrosidasa; trombopoyetina, filgrasima; 20 prostaglandinas; ciclosporina; vasopresina; cromolina sódica (cromoglicato de sodio o de disodio); vancomicina; desferrioxamina (DFO); hormona paratiroides (PTH), incluyendo sus fragmentos; antimicrobianos, incluyendo agentes antifúngicos; vitaminas; análogos, fragmentos, miméticos, o 25 derivados modificados con polietilenglicol (PEG) de estos

compuestos; o cualquier combinación de los mismos.

El agente farmacológicamente activo preferido es un péptido farmacológicamente activo, en particular calcitonina. Una clase conocida de agentes farmacológicamente activos, las
5 calcitoninas, tienen una utilidad farmacéutica variable, y se emplean comúnmente en el tratamiento de, por ejemplo, enfermedad de Paget, hipercalcemia, y osteoporosis post-menopáusica. Diferentes calcitoninas, incluyendo la calcitonina de salmón, de cerdo, y de anguila, están
10 comercialmente disponibles y se emplean comúnmente para el tratamiento de, por ejemplo, enfermedad de Paget, hipercalcemia maligna, y osteoporosis. La calcitonina puede ser cualquier calcitonina, incluyendo sus fuentes naturales, sintéticas, o recombinantes, así como derivados de
15 calcitonina, tales como 1,7-Asu-calcitonina de anguila. Las composiciones pueden comprender una sola calcitonina, o cualquier combinación de dos o más calcitoninas. La calcitonina preferida es la calcitonina de salmón sintética.

Las calcitoninas están comercialmente disponibles o
20 se pueden sintetizar mediante métodos conocidos.

La cantidad de agente farmacológicamente activo es en general una cantidad efectiva para llevar a cabo el propósito pretendido, por ejemplo una cantidad terapéuticamente efectiva. Sin embargo, la cantidad puede ser
25 menor que esa cantidad cuando se vayan a administrar una

pluralidad de las composiciones, es decir, la cantidad efectiva total se puede administrar en unidades de dosificación acumulativas. La cantidad de agente activo también puede ser mayor que la cantidad efectiva cuando la
5 composición proporcione una liberación sostenida del agente farmacológicamente activo. La cantidad total de agente activo que se vaya a utilizar, se puede determinar mediante métodos conocidos por los expertos en la materia. Sin embargo, debido a que las composiciones pueden suministrar el agente activo
10 de una manera más eficiente que las composiciones anteriores, se pueden administrar cantidades menores del agente activo que las utilizadas en las formas de unidades de dosificación anteriores o en los sistemas de suministro anteriores, a un sujeto, mientras que todavía se logren los mismos niveles en
15 sangre y/o efectos terapéuticos.

Cuando el agente farmacológicamente activo es calcitonina de salmón, la dosificación apropiada, por supuesto, variará dependiendo, por ejemplo, del huésped y de la naturaleza y severidad de la condición que se esté
20 tratando. Sin embargo, en general se obtendrán resultados satisfactorios sistémicamente en dosificaciones diarias de aproximadamente 0.5 microgramos/kilogramo a aproximadamente 10 microgramos/kilogramo de peso del cuerpo del animal, de preferencia de 1 microgramo/kilogramo a aproximadamente 6
25 microgramos/kilogramo de peso corporal.

El agente farmacológicamente activo comprende en general del 0.05 al 70 por ciento en peso en relación con el peso total de la composición farmacéutica global, de preferencia una cantidad del 0.01 al 50 por ciento en peso, 5 más preferiblemente del 0.3 al 30 por ciento en peso en relación con el peso total de la composición farmacéutica global.

La crospovidona puede ser cualquier crospovidona. La crospovidona es un homopolímero reticulado sintético de N- 10 vinil-2-pirrolidona, también denominada 1-etenil-2-pirrolidona, que tiene un peso molecular de 1,000,000 o mayor. Las crospovidonas comercialmente disponibles incluyen Poliplasdona XL, Poliplasdona XL-10, Poliplasdona INF-10 disponibles en ISP, Kollidon CL disponible en BASF 15 Corporation. La crospovidona preferida es Poliplasdona XL.

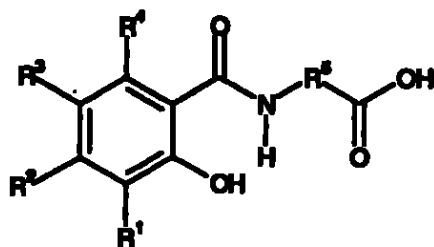
La povidona es un polímero sintético que consiste en grupos 1-vinil-2-pirrolidinona lineales que tienen un peso molecular generalmente entre 2,500 y 3,000,000. Las povidonas comercialmente disponibles incluyen Kollidon K-30, Kollidon 20 K-90F disponibles en BASF Corporation, y Plasdona K-30 y Plasdona K-29/32 disponibles en ISP.

Como se mencionó anteriormente, las crospovidonas y povidonas están comercialmente disponibles. De una manera alternativa, se pueden sintetizar mediante procesos 25 conocidos.

La crospovidona, la povidona, o la combinación de las mismas, generalmente están presentes en las composiciones en una cantidad del 0.5 al 50 por ciento en peso en relación con el peso total de la composición farmacéutica global, de preferencia una cantidad del 2 al 25 por ciento, más preferiblemente del 5 al 20 por ciento en peso en relación con el peso total de la composición farmacéutica.

Los agentes de suministro útiles en la presente invención son cualesquiera agentes útiles para suministrar el agente farmacológicamente activo particular. Los agentes de suministro adecuados son cualquiera de los 123 aminoácidos modificados dados a conocer en la Patente de los Estados Unidos de Norteamérica Número 5,866,536 anteriormente mencionada, o cualquiera de los 193 aminoácidos modificados descritos en la Patente de los Estados Unidos de Norteamérica Número 5,773,647 anteriormente mencionada, o cualquier combinación de los mismos. El contenido de las Patentes de los Estados Unidos de Norteamérica Números 5,773,647 y 5,866,536 anteriormente mencionadas, se incorpora a la presente como referencia en su totalidad. En adición, el agente de suministro puede ser la sal disódica de cualquiera de los aminoácidos modificados anteriormente mencionados, así como solvatos de etanol y sus hidratos. Los compuestos adecuados incluyen los compuestos de la siguiente fórmula I:

5



Fórmula I

en donde:

10 R^1 , R^2 , R^3 , y R^4 son independientemente hidrógeno, -OH, $-NR^6R^7$, halógeno, alquilo de 1 a 4 átomos de carbono, o alcoxilo de 1 a 4 átomos de carbono;

R^5 es un alquilenno de 2 a 16 átomos de carbono sustituido o insustituido, alquenileno de 2 a 16 átomos de
15 carbono sustituido o insustituido, alquilo de 1 a 12 átomos de carbono-(arileno) sustituido o insustituido, o arilo(alquilenno de 1 a 12 átomos de carbono) insustituido o insustituido; y

R^6 y R^7 son independientemente hidrógeno, oxígeno, o
20 alquilo de 1 a 4 átomos de carbono; y sus hidratos y solvatos de alcohol. Los compuestos de la fórmula I, así como sus sales disódicas y sus solvatos de alcohol e hidratos, se describen en la Publicación Internacional Número WO 00/059863, junto con los métodos para su preparación.

25 La sal disódica se puede preparar a partir del

solvato de etanol mediante la evaporación o secado del solvato de etanol mediante métodos conocidos en la técnica para formar la sal disódica anhidra. El secado se lleva generalmente a cabo a una temperatura de aproximadamente 80°C a aproximadamente 120°C, de preferencia de aproximadamente 85°C a aproximadamente 90°C, y más preferiblemente a aproximadamente 85°C. El paso de secado se lleva a cabo en general a una presión de 660 mm Hg o mayor. La sal disódica anhidra contiene en general menos de aproximadamente el 5 por ciento en peso de etanol, y de preferencia menos de aproximadamente el 2 por ciento en peso de etanol, basándose en un peso total del 100 por ciento de la sal disódica anhidra.

La sal disódica del agente de suministro también se puede preparar haciendo una pasta del agente de suministro en agua, y agregando dos equivalentes molares de hidróxido de sodio acuoso, alcóxido de sodio, o similar. Los alcóxidos de sodio adecuados incluyen, pero no se limitan a, metóxido de sodio, etóxido de sodio, y combinaciones de los mismos.

Un método todavía adicional para preparar la sal disódica es mediante la reacción del agente de suministro con un equivalente molar de hidróxido de sodio, para dar la sal disódica.

La sal disódica se puede aislar como un sólido mediante la concentración de la solución que contenga a la

sal disódica hasta una pasta espesa mediante destilación al vacío. Esta pasta se puede secar en un horno al vacío para obtener la sal disódica del agente de suministro como un sólido. El sólido también se puede aislar mediante secado por
5 pulverización de una solución acuosa de la sal disódica.

Los agentes de suministro se pueden preparar mediante métodos conocidos en este campo, por ejemplo como se mencionó anteriormente, mediante los métodos descritos en las Patentes de los Estados Unidos de Norteamérica Números
10 5,773,647 y 5,866,536.

Los solvatos de etanol, como se describen en la Publicación Internacional Número WO 00/059863 anteriormente mencionada, incluyen, pero no se limitan a, un complejo molecular o iónico de moléculas o iones de solvente de etanol
15 con moléculas o iones de la sal disódica del agente de suministro. Normalmente, el solvato de etanol contiene aproximadamente una molécula o ion de etanol por cada molécula de sal disódica del agente de suministro.

El solvato de etanol de la sal disódica del agente
20 de suministro se puede preparar mediante la disolución del agente de suministro en etanol. Normalmente, cada gramo del agente de suministro se disuelve en de aproximadamente 1 a aproximadamente 50 mililitros de etanol, y en general de aproximadamente 2 a aproximadamente 10 mililitros de etanol.
25 Luego se hace reaccionar la solución de agente de

suministro/etanol con un exceso molar de una sal que contenga sodio, tal como una sal que contenga monosodio; en relación con el agente de suministro, es decir, por cada mol de agente de suministro hay más de un mol de cationes de sodio, produciendo el solvato de etanol. Las sales monosódicas adecuadas incluyen, pero no se limitan a, hidróxido de sodio; alcóxidos de sodio, tales como metóxido de sodio y etóxido de sodio; y cualquier combinación de los anteriores. De preferencia, se agregan cuando menos aproximadamente 2 equivalentes molares de la sal que contenga monosodio a la solución de etanol, es decir, por cada mol de agente de suministro hay cuando menos aproximadamente 2 moles de cationes de sodio. En general, la reacción se lleva a cabo en o debajo de la temperatura de reflujo de la mezcla, tal como a temperatura ambiente. Luego se recupera el solvato de etanol mediante métodos conocidos en la técnica, tales como concentración de la pasta resultante con destilación atmosférica, enfriamiento de la pasta concentrada, y filtración del sólido. Entonces el sólido recuperado se puede secar al vacío para obtener el solvato de etanol.

Los hidratos de las sales disódicas de los agentes de suministro se pueden preparar secando el solvato de etanol para formar una sal disódica anhidra, como se describió anteriormente, e hidratando la sal disódica anhidra. De preferencia, se forma el monohidrato de la sal disódica.

Debido a que la sal disódica anhidra es muy hidróscopica, se forma el hidrato al exponerse a la humedad atmosférica. En general, el paso de hidratación se realiza desde aproximadamente la temperatura ambiente hasta aproximadamente 5 50°C, de preferencia desde la temperatura ambiente hasta aproximadamente 30°C, y en un medio ambiente que tenga cuando menos el 50 por ciento de humedad relativa. De una manera alternativa, la sal disódica anhidra se puede hidratar con vapor.

10 Los agentes de suministro preferidos son ácido N-(5-clorosaliciloil)-8-aminocaprílico (5-CNAC), ácido N-(10-[2-hidroxibenzoil]aminodecanoico (SNAD), ácido N-(8-[2-hidroxibenzoil]amino)caprílico (SNAC), y sus sales monosódicas y disódicas, solvatos de etanol de sus sales 15 sódicas, y los monohidratos de sus sales sódicas, y cualesquiera combinaciones de los mismos. El agente de suministro más preferido es la sal disódica de 5-CNAC y su monohidrato.

Las composiciones farmacéuticas de la presente 20 invención normalmente contienen una cantidad de suministro efectiva de uno o más de los agentes de suministro, es decir, una cantidad suficiente para suministrar el agente activo para el efecto deseado. En general, el agente de suministro está presente en una cantidad del 2.5 por ciento al 99.4 por 25 ciento en peso, más preferiblemente del 25 por ciento al 50

por ciento en peso.

Las composiciones farmacéuticas de la presente invención se pueden proporcionar como una cápsula, incluyendo una cápsula de gel blanda, tableta, caplet, u otra forma de
5 dosificación oral sólida, por ejemplo supositorio, todas las cuales se pueden preparar mediante métodos bien conocidos en este campo.

Las composiciones pueden comprender adicionalmente aditivos en las cantidades empleadas por costumbre,
10 incluyendo, pero no limitándose a, un ajustador del pH, un conservador, un saborizante, un agente enmascarador del sabor, una fragancia, un humectante, un tónico, un colorante, un tensoactivo, un plastificante, un lubricante tal como estearato de magnesio, un auxiliar de flujo, un
15 auxiliar de compresión, un solubilizante, un excipiente, un diluyente tal como celulosa microcristalina, por ejemplo Avicel PH 102 suministrada por FMC Corporation, o cualquier combinación de los mismos. Otros aditivos pueden incluir sales reguladoras de fosfato, ácido cítrico, glicoles, y
20 otros agentes dispersantes.

La composición también puede incluir uno o más inhibidores de enzimas, tales como actinonina o epiactinonina y sus derivados; aprotinina, el inhibidor de Trasylol and Bowman-Birk.

25 Además, puede haber un inhibidor de transporte

presente, es decir, una β -glicoproteína, tal como Cetoprofina, en las composiciones de la presente invención.

De preferencia, las composiciones farmacéuticas sólidas de la presente invención incluyen un diluyente, tal como Avicel, y un lubricante, tal como estearato de magnesio.

Las composiciones farmacéuticas sólidas de la presente invención se pueden preparar mediante métodos convencionales, por ejemplo mezclando una mezcla del agente activo o de los agentes activos, el agente de suministro, la crospovidona o povidona, y otros ingredientes, amasando, y llenando en cápsulas, o en lugar de llenar en cápsulas, moldeando seguido por formación de tabletas adicional o moldeo por compresión para dar tabletas. En adición, se puede formar una dispersión sólida mediante los métodos conocidos, seguida por el procesamiento adicional para formar una tableta o cápsula.

De preferencia, los ingredientes de las composiciones farmacéuticas de la presente invención se mezclan de una manera homogénea o uniforme a través de toda la forma de dosificación sólida.

Las composiciones de la presente invención se puede administrar para suministrar un agente activo a cualquier animal que lo necesite, incluyendo, pero no limitándose a, mamíferos, tales como roedores, vacas, cerdos, perros, gatos, y primates, en particular seres humanos.

Los siguientes ejemplos sirven para ilustrar adicionalmente la invención.

EJEMPLO 1

Se prepararon tabletas de acuerdo con la presente invención (EJEMPLO A), así como los EJEMPLOS COMPARATIVOS B y C que utilizan Ac-Di-Sol en lugar de la crospovidona (Ac-Di-Sol es carboximetilcelulosa de sodio reticulada), y el EJEMPLO COMPARATIVO D, que es una cápsula co-liofilizada que contiene 5-CNAC y calcitonina de salmón.

Específicamente, las tabletas se preparan como sigue:

Preparación del Ejemplo A

Se combinan 0.502 gramos de calcitonina de salmón, previamente tamizada a través de un tamiz de malla 40, 120 gramos de sal disódica de 5-CNAC, previamente tamizada a través de un tamiz de malla 35, y 20 gramos de Poliplasdon XL (crospovidona, NF), en un matraz de 500 mililitros, y se mezclan utilizando una mezcladora Turbula durante 2 minutos a una velocidad de 46 RPM. Se agregan 125.4 gramos adicionales de sal disódica de 5-CNAC, previamente tamizada a través de un tamiz de malla 35, y 32.5 gramos de Avicel PH 102 al matraz, y se mezclan durante un período de 8 minutos a una velocidad de 46 RPM. Se agregan 32.5 gramos adicionales de Avicel al matraz, y se mezclan durante 5 minutos a una

velocidad de 46 RPM. Se tamizan 4.0 gramos de estearato de magnesio adentro del matraz utilizando un tamiz de malla 35, y se mezclan durante 1 minuto a una velocidad de 46 RPM. La mezcla final se comprime en tabletas utilizando una prensa de tabletas Manesty B3B. El peso de la tableta es de aproximadamente 400 miligramos.

Ejemplo Comparativo B

Se combinan 14 gramos de la sal disódica de 5-CNAC y 0.56 gramos de CabOSil, y se tamizan a través de un tamiz de malla 40. Se combinan 0.3 gramos la mezcla de sal disódica de 5-CNAC/CabOSil, 0.028 gramos de calcitonina de salmón, previamente tamizada a través de un tamiz de malla 40, y 0.56 gramos de Ac-Di-Sol, previamente tamizado a través de un tamiz de malla 30, en una mezcladora-V de 1 cuarto. La mezcla se bate durante 2 minutos. Se agregan aproximadamente 14.3 gramos de la mezcla de sal disódica de 5-CNAC/Cab-O-Sil geométricamente a la mezcladora-V, y se mezclan durante 2 minutos después de cada adición (se agregan en sucesión aproximadamente 0.8, 1.7, 3.2, y 8.6 gramos). Se agregan 12.43 gramos de Avicel PH 102 y 0.42 gramos de estearato de magnesio, previamente tamizados a través de un tamiz de malla 40, a la mezcladora-V, y se mezclan durante 5 minutos. Luego se tamiza la mezcla final a través de un tamiz de malla 40, y se comprime en tabletas utilizando, por ejemplo, una prensa

Manesty F3. Los pesos de las tabletas son de aproximadamente 400 miligramos.

Ejemplo Comparativo C

0.1224 gramos de calcitonina de salmón, previamente
5 tamizada a través de un tamiz de malla 40, 30 gramos de sal
disódica de 5-CNAC, previamente tamizada a través de un tamiz
de malla 35, y 4 gramos de Ac-Di-Sol, se colocan en un matraz
Pyrex® de 500 mililitros, y se mezclan utilizando una
mezcladora Turbula durante 2 minutos a una velocidad de 46
10 RPM. Se agregan 31.35 gramos adicionales de sal disódica de
5-CNAC, previamente tamizada a través de un tamiz de malla
35, y 15 gramos de Avicel PH 102 al matraz, y se mezclan
durante un período de 8 minutos a una velocidad de 46 RPM.
Se combinan 2 gramos de CabOSil y 16.15 gramos de Avicel, y
15 se tamizan a través de un tamiz de malla 18. La mezcla de
CabOSil/Avicel se agrega al matraz, y se mezcla durante 5
minutos a una velocidad de 46 RPM. Se tamizan 1.5 gramos de
estearato de magnesio en el matraz utilizando un tamiz de
malla 35, y se mezclan durante 2 minutos a una velocidad de 46
20 RPM. La mezcla final se comprime en tabletas utilizando una
prensa de tabletas Manesty B3B. Los pesos de las tabletas son
de aproximadamente 400 miligramos.

Ejemplo Comparativo D

25 Se agregan 18 kilogramos de agua para inyección y

0.16 kilogramos de hidróxido de sodio, NF, a un recipiente, y se mezclan hasta disolverse. Se agregan 0.800 kilogramos del ácido libre de 5-CNAC al recipiente, y se agitan a 400-600 RPM durante un mínimo de 10 minutos. El pH del recipiente se
5 ajusta a aproximadamente 8.5 utilizando hidróxido de sodio 10N. El recipiente se agita durante un mínimo de 10 minutos después de cada adición de hidróxido de sodio 10N. El hidróxido de sodio 10N se prepara agregando 40 gramos de hidróxido de sodio, NF, a 100 mililitros de agua para
10 inyección. El peso final de la solución mezclada se ajusta a 20.320 kilogramos mediante la adición de agua para inyección (densidad de 1.016). El recipiente se agita a 400-600 RPM durante un mínimo de 30 minutos. La solución mezclada se filtra en otro recipiente utilizando una bomba peristáltica,
15 tubería de silicona, y un filtro de cápsula de membrana MPHL de 0.45 micras DuraPore.

Se prepara una solución de regulador de fosfato agregando 13.8 gramos de monohidrato de fosfato monosódico, USP, a 900 gramos de agua para inyección, y ajustando a un pH
20 de 4.0 utilizando una solución de ácido fosfórico 1.0N. La solución de ácido fosfórico se prepara agregando 0.96 gramos de ácido fosfórico, NF, a 25 mililitros de agua para inyección. El peso final de la solución de regulador de fosfato se ajusta a 1,007 gramos (densidad de 1.007),
25 utilizando agua para inyección, y se agita durante 5 minutos.

Se prepara una solución regulada de calcitonina de salmón agregando 1.6 gramos de calcitonina de salmón a 660 gramos de solución reguladora de fosfato. El peso final de la solución se ajusta hasta un peso final de 806.4 gramos
5 (densidad de 1.008), utilizando la solución reguladora de fosfato, y se mezcla durante un mínimo de 5 minutos a una velocidad de 250 RPM o menos.

Se agregan por goteo 0.800 kilogramos de solución regulada de calcitonina de salmón a 20 kilogramos de la
10 solución de 5-CNAC con mezcla constante a una velocidad de 250 RPM o menos, durante un mínimo de 5 minutos.

Se suministran aproximadamente 0.75 litros de solución de calcitonina de salmón/5-CNAC a charolas de liofilización de acero inoxidable (30.5 x 30.5 centímetros)
15 para una profundidad final de la solución de 0.8-0.9 centímetros. Se llenan aproximadamente 29 charolas con 21.75 litros de solución de calcitonina de salmón/5-CNAC. Las charolas se colocan en una secadora de congelación Edwards, y se liofilizan de acuerdo con el siguiente procedimiento:

20 1. Cuando se cargan las charolas y se sella la secadora Reeze, se enfrían los anaqueles a una velocidad de 1°C/minuto.

2. Una vez que la temperatura del anaquel alcanza -45°C, se mantiene la temperatura del anaquel a -45°C durante
25 un mínimo de 120 minutos.

3. Se enfría el condensador hasta -50°C o más baja.
4. Se evacua la cámara, y cuando se mantiene un vacío de 300 micras, se eleva la temperatura del anaquel hasta -30°C a una velocidad de 1°C por minuto.
- 5 5. Se mantiene la temperatura del anaquel a -30°C durante 180 minutos.
6. Se reduce la presión en la cámara hasta 200 micras, y cuando se mantiene un vacío de 200 micras, se eleva la temperatura del anaquel a -20°C a una velocidad de 1°C por
10 minuto.
7. Se mantiene la temperatura del anaquel a -20°C durante 200 minutos.
8. Se eleva la temperatura del anaquel a -10°C a una velocidad de 1°C por minuto.
- 15 9. Se mantiene la temperatura del anaquel a -10°C durante 360 minutos.
10. Se eleva la temperatura del anaquel a 0°C a una velocidad de 1°C por minuto.
11. Se mantiene la temperatura del anaquel a 0°C
20 durante 720 minutos.
12. Se reduce la presión en la cámara hasta 100 micras, y cuando se mantiene un vacío de 100 micras, se eleva la temperatura del anaquel a $+10^{\circ}\text{C}$ a una velocidad de 1°C por minuto.
- 25 13. Se mantiene la temperatura del anaquel a $+10^{\circ}\text{C}$

durante 540 minutos.

14. Se eleva la temperatura del anaquel a +25°C a una velocidad de 1°C por minuto.

15. Se mantiene la temperatura del anaquel a +25°C
5 durante 440 minutos.

16. Se libera el vacío y se descargan las charolas.

Se remueve la solución de calcitonina de salmón/5-CNAC co-liofilizada de las charolas, y se almacena en bolsas de polietileno y lámina bajo refrigeración. Se suministran
10 aproximadamente 400 miligramos de material co-liofilizado a cápsulas (tamaño AA) para su administración.

Ejemplo 2

Administración a Primates

15 Las tabletas o cápsulas preparadas en el Ejemplo 1 se administran a monos Rhesus como sigue: de 4 a 6 monos de un grupo fueron dosificados cada uno ya sea con una cápsula o con dos tabletas del Ejemplo 1 como sigue:

Los monos Rhesus se ponen en ayunas durante la
20 noche antes de la dosificación, y se restringen en sillas completamente conscientes, por la duración del período de estudio. Las cápsulas o tabletas se administran mediante un tubo de alimentación, seguidas por 10 mililitros de agua.

Se recolectan muestras de sangre a las 0.25, 0.5,
25 0.75, 1, 1.5, 2, 3, 4, 5, y 6 horas después de la

administración. La calcitonina de salmón en plasma se determina mediante radioinmunoensayo. Los resultados de calcitonina de salmón en plasma de los primates (sCT) de cada grupo de monos se promedia, y se calculan los resultados de la máxima concentración media de calcitonina en plasma y del área debajo de la curva (AUC), y se reportan en la Tabla 1.

TABLA 1

Forma de Dosificación	sCT Cmax (pg/mL)	sCT AUC
EJEMPLO COMPARATIVO D	415	792.4
EJEMPLO COMPARATIVO B	457	992.5
EJEMPLO COMPARATIVO C	329	797
EJEMPLO A	2420	4400

15

Como se puede ver en los datos de la Tabla 1, la Cmax de calcitonina de salmón y la AUC de calcitonina de salmón son mucho mayores para la composición de acuerdo con la presente invención, que contiene la crospovidona (Ejemplo A), contra las composiciones comparativas que no contienen crospovidona, dando como resultado una biodisponibilidad oral muy mejorada de las formulaciones de conformidad con la presente invención.

25

Ejemplo 3

Prueba de Estabilidad Acelerada

Se preparan tabletas conteniendo 0.065 miligramos, 0.400 miligramos, y 2.500 miligramos de sCT de acuerdo con el Ejemplo Comparativo C y el Ejemplo A, respectivamente, ajustándose la sCT y el Avicel con el objeto de obtener las concentraciones objetivo. Las tabletas se colocan en una botella de polietileno de alta densidad con un desecante, la cual se sella por inducción y se tapa. Se conducen pruebas de estabilidad acelerada colocando las muestras de estabilidad en cámaras ambientales a 25°C y con el 60 por ciento de humedad relativa, las muestras se llevan hasta los puntos del tiempo especificados, es decir, a 3, 4, y 6 semanas, y se analizan para determinar la sCT mediante cromatografía de líquidos de alto rendimiento. Los resultados se muestran en la Tabla 2.

TABLA 2

Ensayo de sCT	Tableta de 0.065 mg		Tableta de 0.400 mg		Tableta de 2.500 mg	
	Ejemplo Comparativo C	Ejemplo A	Ejemplo Comparativo C	Ejemplo A	Ejemplo Comparativo C	Ejemplo A
25°C/60% RH						
Tiempo 0	93.5%	100.9%	94.3%	103.0%	100.3%	98.0%
3 semanas	-	97.4%	-	98.8%	-	-
4 semanas	84.2%	-	88.8%	-	91.5%	100.2%
6 semanas	-	95.2%	-	96.9%	-	-

La comparación del Ejemplo Comparativo C después de 4 semanas (aproximadamente una reducción del 10 por ciento en el ensayo de sCT) con el Ejemplo A de acuerdo con la presente invención después de 6 semanas (aproximadamente una reducción del 5 por ciento en el ensayo de sCT), ambos a temperatura ambiente, demuestra que la formulación de conformidad con la presente invención da como resultado una mejor estabilidad de las tabletas preparadas de acuerdo con la presente invención.

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Ejemplo 4

Se determinó la desintegración de las tabletas de las formulaciones sólidas mediante la preparación de tabletas de acuerdo con el Ejemplo 1, conteniendo el 60 por ciento de sal disódica de 5-CNAC, el 29 por ciento de Avicel, el 1 por ciento de estearato de magnesio, pero excluyendo la sCT. La desintegración de la tableta se determinó de acuerdo con la Prueba de Desintegración USP <701>, mientras que la dureza de la tableta se determinó utilizando un Probador de Dureza de Tabletado calibrado Vector/Schleuniger 6D. Los resultados se muestran en la Tabla 3.

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TABLA 3

	Excipiente	Contenido	Dureza	Desintegración	Dureza	Desintegración
	Ac-Di-Sol	10%	5.7 Kp*	1.1-1.4 min.	10.1 Kp	5.6-6.5 min.
5	Explotab	10%	6.9 Kp	2.6-3.3 min.	10.3 Kp	6.5-7.5 min.
	Poliplasdona XL	10%	7.3 Kp	0.6-0.8 min.	10.5 Kp	2.4-2.7 min.
	Ac-Di-Sol(Cab-O-Sil)*	10%	6.3 Kp	4.3-5.3 min.	10.3 Kp	7.3-8.0 min.

*Kp = kilopascales.

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Los resultados de la Tabla 3 indican que el uso de Poliplasdona XL (crospovidona) en combinación con el 5-CNAC, produjo la desintegración más rápida en relación con las tabletas preparadas utilizando 5-CNAC en combinación con
15 otros excipientes, indicando una mejor liberación del agente farmacológicamente activo a partir de las formulaciones sólidas de acuerdo con la presente invención.

Ejemplo 5

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Estabilidad Química

Se preparan muestras para la prueba de estabilidad en tensión extrema, colocando las tabletas (preparadas de una manera análoga a aquéllas del Ejemplo 1 anterior, utilizando la proporción de ingredientes indicada en la Tabla 4), en una
25 botella ámbar tapada. Se conducen pruebas de estabilidad

aceleradas colocando las muestras en un horno calibrado a 60°C. Las muestras se analizan para determinar la sCT inicialmente, y después ya sea de 3 ó 4 días, como se especifica mediante cromatografía de líquidos de alto
5 rendimiento. Los resultados se muestran en la Tabla 4.

TABLA 4

10	Excipientes (0.4 mg sCT/200 mg sal disódica de 5- CNAC)	60°C	Ensayo de sCT Inicial	Ensayo de sCT con Tensión	% de Cambio
	Ac-Di-Sol, Cab-O-Sil, Avicel, Estearato de Magnesio (EJEMPLO COMPARATIVO C)	3 días	94.0%	12.3%	-81.7%
15	10% Poliplasdona XL-10, Avicel, Estearato de Magnesio (Ejemplo A)	4 días	98.3%	86.5%	-11.8%

Como se puede ver en la Tabla 4, la estabilidad química de la sCT bajo condiciones de tensión extrema mejoró
20 con la formulación de la presente invención (Ejemplo F) que contenía crosprovidona (Poliplasdona XL-10), comparándose con la formulación comparativa sin crosprovidona.

Lo anterior muestra claramente que las composiciones de conformidad con la presente invención tienen
25 una biodisponibilidad oral considerablemente mejorada del

agente activo, en particular calcitonina, en relación con otras formulaciones orales, buenas velocidades de desintegración, y una excelente estabilidad.

Las modalidades y ejemplos anteriores se dan
5 meramente para ilustrar la presente invención, y no pretenden ser limitantes. Otras numerosas modalidades y variaciones están dentro del alcance de la invención, y están fácilmente accesibles para los expertos en la materia.

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REIVINDICACIONES

1. Una composición farmacéutica sólida adecuada para el suministro oral de un agente farmacológicamente
5 activo, la cual comprende:

a. una cantidad terapéuticamente efectiva de un agente farmacológicamente activo;

b. una crospovidona o povidona; y

c. un agente de suministro para este agente
10 farmacológicamente activo.

2. Una composición de acuerdo con la reivindicación 1, en donde el agente activo es un péptido.

3. Una composición de acuerdo con la reivindicación 1 ó 2, en donde el péptido es una calcitonina.

15 4. Una composición de acuerdo con la reivindicación 3, en donde la calcitonina es calcitonina de salmón.

5. Una composición de acuerdo con cualquiera de las reivindicaciones anteriores, la cual comprende
20 crospovidona.

6. Una composición de acuerdo con cualquiera de las reivindicaciones anteriores, en donde el agente de suministro es 5-CNAC.

7. Una composición de acuerdo con cualquiera de
25 las reivindicaciones anteriores, en donde el agente de suministro es la sal disódica de 5-CNAC.

8. Una composición de acuerdo con cualquiera de las reivindicaciones anteriores, la cual incluye adicionalmente un diluyente.

9. Una composición de acuerdo con la
5 reivindicación 8, en donde el diluyente es celulosa microcristalina.

10. Una composición de acuerdo con cualquiera de las reivindicaciones anteriores, la cual incluye adicionalmente un lubricante.

10 11. Una composición de acuerdo con la reivindicación 10, en donde el lubricante es estearato de magnesio.

12. Un método para mejorar la biodisponibilidad oral de un agente farmacológicamente activo, comprendiendo
15 este método administrar a un paciente que necesite un agente farmacológicamente activo, una cantidad efectiva de una composición farmacéutica de acuerdo con cualquiera de las reivindicaciones anteriores.

13. Un método de tratamiento de enfermedades
20 relacionadas con los huesos y desórdenes de calcio, el cual comprende administrar a un paciente que necesite dicho tratamiento, una cantidad terapéuticamente efectiva de una composición de acuerdo con cualquiera de las reivindicaciones 1 a 11, en donde este agente farmacológicamente activo es
25 calcitonina.

14. Un método de acuerdo con la reivindicación 13, en donde la calcitonina es calcitonina de salmón.

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RESUMEN

Se dan a conocer composiciones farmacéuticas sólidas adecuadas para el suministro oral de agentes farmacológicamente activos, por ejemplo péptidos, las cuales comprenden una cantidad terapéuticamente efectiva de un agente farmacológicamente activo; una crospovidona o povidona; y un agente de suministro para este agente farmacológicamente activo. Las composiciones proporcionan una excelente biodisponibilidad oral de los agentes farmacológicamente activos, en particular calcitonina.

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REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
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	()	()

COMPLETA () INCOMPLETA ()

DISEÑO INDUSTRIAL ()

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

COMPLETA () INCOMPLETA ()

ESQUEMA DE TRAZADO ()

Indicación de que 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	()	()

COMPLETA () INCOMPLETA ()

Firma Responsable



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