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DELEGATURA PROPIEDAD INDUSTRIAL

División de Nuevas Creaciones



SOLICITUD

PCT

PATENTE DE INVENCION

ENTRADA EN FASE NACIONAL

001-8313

21. EXPEDIENTE No.

54. TITULO

COMPOSICIÓN FARMACÉUTICA QUE CONTIENE BICALUTAMIDA  
Y UN MÉTODO PARA SU USO

51. CLASIFICACION INTERNACIONAL

71. SOLICITANTE

PANACEA BIOTEC LTD.

DOMICILIO

MAHARASHTRA, INDIA

74. APODERADO

JUAN PABLO CADENA SARMIENTO

22. SANTAFE DE BOGOTA, D.C.

## PETITORIO

AS: 109.339

Industria y Comercio  
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 09-008313- -00000-0000

Fecha: 2009-01-29 16:34:09 Dep. 2020 NUECREACIONE  
Tra. 11 PATENTEIYII Eje: 379 FASENACIONALII  
Act. 411 PRESENTACION Folios: 99FORMULARIO 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

Nombre: **PANACEA BIOTEC LTD.**Dirección: 201, Samarpan Complex, New-Link  
Road, Chakala, Andheri(E), Mumbai 400 099,  
Maharashtra, India

Nacionalidad o Domicilio: India

Lugar de Constitución: India

Teléfono:

Fax:

E-mail

## IDENTIFICACIÓN

C.C. ☐NIT ☐C.E. ☐Otro ☐

Cual \_\_\_\_\_

Número \_\_\_\_\_

3

REPRESENTANTE  
O APODERADO

Nombre: JUAN PABLO CADENA SARMIENTO

Dirección: Cra. 7 No. 71-21 Torre B – Piso 4,  
Bogotá, Colombia.

Teléfono: 744-2200

Fax: 742-2200

E-mail:

## IDENTIFICACIÓN

C.C. ☒NIT ☐C.E. ☐Otro ☐

Cual \_\_\_\_\_

Número 80.410.337 TP 57492

4

INVENTOR (ES)  
(72)

Nombre: Amarjit SINGH, Sarabjit SINGH, Shivanand PUTHLI.

Dirección: 301, Prinnacle-d-Pride, 3rd Road, Off Turner Road, Bandra (West), Mumbai 400  
050, Maharashtra, IN; House No. 1252, Sector 42/B, Chandigarh 160 036, IN; 201,  
Samarpan Complex, New-Link Road, Chakala, Andheri (E), Mumbai-400099, Maharashtra,  
IN (Respectivamente).

Nacionalidad o Domicilio: India

## 5 PCT (86)

Solicitud Internacional No.

PCT/IN2007/00274

Fecha

05-07-2007

Publicación Internacional No

WO/2008/068770 A3

Fecha

12-06-20086 Título (54): **COMPOSICIÓN FARMACEUTICA QUE CONTIENE BICALUTAMIDA Y UN MÉTODO PARA  
SU USO**

## 7 Clasificación Internacional (51): \_\_\_\_\_

## 8 Prioridad

SI ☒NO ☐

(33) País de Origen

IN

(32) Fecha

07-07-2006

(31) Número de Solicitud

1074/MUM/2006

9 Comprobante de pago No. 08-96,480; 09-1,113; 08-87,524; 08-90,551; 08-87,539; 09-1,221Fecha 27-01-2009

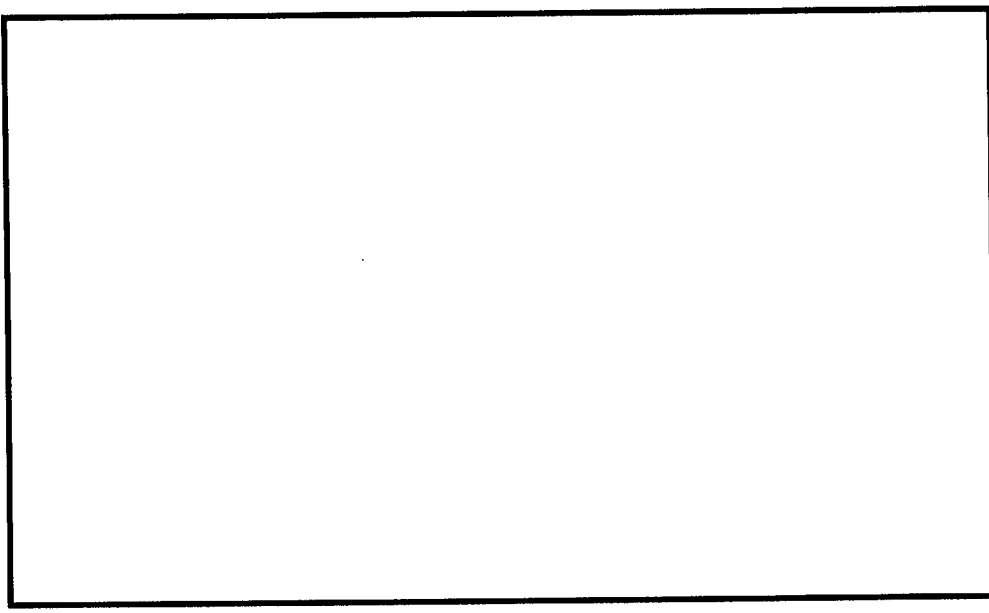
Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

10

ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud. \$ 540.000
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso. **Fotocopia autenticada**
- ☐ Documento de cesión del inventor al solicitante o a su causante.
- ☒ 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 de examen preliminar internacional efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☐ Arte final 12x12.
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☐ De ser el caso, modificaciones efectuadas a la solicitud internacional.
- ☒ Otros: Tarjeta de Propietarios  
Documentos PCT  
Comprobante(s) de pago de la tasa por concepto de Reivindicaciones adicionales. \$225.000  
(9\*\$25.000)

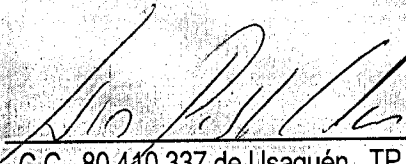
11 FIGURA CARACTERÍSTICA:



12

Solicito la concesión de la patente,

NOMBRE: JUAN PABLO CADENA SARMIENTO

FIRMA:   
C.C. 80.410.337 de Usaquén TP 57492 del C.S.J.

109 339

3

## SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 09-008313- -00000-0000

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Fecha: 2009-01-29 16:34:09 Dep. 2020 NUECREACIONI  
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALI  
Act. 411 PRESENTACION Folios: 99

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 96,480  
FECHA : DICIEMBRE 12 DE 2008

## \*\*\*\*\* CONSIGNACION \*\*\*\*\*

| DEPOSITANTE           | TIPO PAGO    | BANCO           | CUENTA    | No. PAGO | FECHA PGO  | Vr. PAGO      |
|-----------------------|--------------|-----------------|-----------|----------|------------|---------------|
| BRIGARD & CASTRO LTDA | CONSIGNACION | BANCO DE BOGOTA | 062754387 | 3249923  | 12/12/2008 | 25,011,000.00 |

## \*\*\*\*\* CONCEPTO \*\*\*\*\*

| CANT. | RENTISTICO  | CONCEPTO                            | TOTAL CONCEPTO |
|-------|-------------|-------------------------------------|----------------|
| 1     | 50005-01-01 | SOLICITUDES                         |                |
|       |             | 1 TRAMITES DE SOL. DE PATENTE DE IN | 501,000.00     |
|       |             | TOTAL :                             | \$ 501,000.00  |

SON: QUINIENTOS UN MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No.

109 339

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 1,113  
FECHA : ENERO 6 DE 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 09-008313- -00000-0000

Fecha: 2009-01-29 16:34:09 Dep. 2020 NUECREACIONE  
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII  
Act. 411 PRESENTACION Folios: 99

## \*\*\*\*\* CONSIGNACION \*\*\*\*\*

| DEPOSITANTE           | TIPO PAGO      | BANCO | CUENTA | No. PAGO | FECHA PGO  | Vr. PAGO     |
|-----------------------|----------------|-------|--------|----------|------------|--------------|
| BRIGARD & CASTRO LTDA | RECIBO DE CAJA |       |        | 1039     | 06/01/2009 | 5,012,000.00 |

## \*\*\*\*\* CONCEPTO \*\*\*\*\*

| CANT. | RENTISTICO  | CONCEPTO                              | TOTAL CONCEPTO |
|-------|-------------|---------------------------------------|----------------|
| 1     | 50005-01-09 | OTROS SERVICIOS DE PROPIEDAD I        |                |
|       |             | 998 VALOR COMPLEMENTO TARIFA A#0 ANTR | 39,000.00      |
|       |             | TOTAL :                               | \$ 39,000.00   |

SON: TREINTA Y NUEVE MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

CERTIFICACION DE EXCEDENTE : 08 - 87,524  
 FECHA : NOVIEMBRE 6 DE 2008



No. 09-008313- -00000-0000

Fecha: 2009-01-29 16:34:09 Dep. 2020 NUECREACION  
 Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII  
 Act. 411 PRESENTACION Folios: 99

## \*\*\*\*\* CONSIGNACION \*\*\*\*\*

| DEPOSITANTE           | TIPO PAGO    | BANCO           | CUENTA    | No. PAGO | FECHA PGO  | Vr. PAGO      |
|-----------------------|--------------|-----------------|-----------|----------|------------|---------------|
| BRIGARD & CASTRO LTDA | CONSIGNACION | BANCO DE BOGOTA | 062754387 | 79585914 | 06/11/2008 | 31,842,000.00 |

## \*\*\*\*\* CONCEPTO \*\*\*\*\*

| CANT. | RENTISTICO  | CONCEPTO                           | TOTAL CONCEPTO |
|-------|-------------|------------------------------------|----------------|
| 1     | 50005-01-09 | OTROS SERVICIOS DE PROPIEDAD I     |                |
|       |             | 99 OTROS SERVICIOS ADMINISTRATIVOS | 100,000.00     |
|       |             | TOTAL :                            | \$ 100,000.00  |

ON: CIEN MIL PESOS

RESPONSABLE : \_\_\_\_\_

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. \_\_\_\_\_

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA  
 COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER  
 SUSTITUIDA POR NINGUN RECIBO.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

CERTIFICACION DE EXCEDENTE : 08 - 90,551  
FECHA : NOVIEMBRE 19 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 09-008313- -00000-0000

Fecha: 2009-01-29 16:34:09 Dep. 2020 NUECREACIONE  
Tra. 11 PATENTEIYII Evs: 379 FASENACIONALII  
Act. 411 PRESENTACION Folios: 99

## \*\*\*\*\* CONSIGNACION \*\*\*\*\*

| DEPOSITANTE           | TIPO PAGO    | BANCO           | CUENTA    | No. PAGO | FECHA PGO  | Vr. PAGO      |
|-----------------------|--------------|-----------------|-----------|----------|------------|---------------|
| BRIGARD & CASTRO LTDA | CONSIGNACION | BANCO DE BOGOTA | 062754387 | 97849986 | 19/11/2008 | 25,487,000.00 |

## \*\*\*\*\* CONCEPTO \*\*\*\*\*

| CANT. | RENTISTICO  | CONCEPTO                          | TOTAL CONCEPTO |
|-------|-------------|-----------------------------------|----------------|
| 1     | 50005-01-09 | OTROS SERVICIOS DE PROPIEDAD I    |                |
|       |             | 99 OTROS SERVCIOS ADMINISTRATIVOS | 100,000.00     |
|       |             | TOTAL :                           | \$ 100,000.00  |

SON: CIENTO MIL PESOS

RESPONSABLE : \_\_\_\_\_

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. \_\_\_\_\_

ESTA CERTIFICACION DE EXCEDENTE DE PAGO SOLO PODRA SER UTILIZADA  
COMO PARTE DE LA CANCELACION DE UNA TARIFA VIGENTE Y NO PODRA SER  
SUSTITUIDA POR NINGUN RECIBO.

109 339<sup>7</sup>

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 87,539  
FECHA : NOVIEMBRE 6 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 09-008313- -00000-0000

Fecha: 2009-01-29 16:34:09 Dep. 2020 NUECREACIONI  
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII  
Act. 411 PRESENTACION Folios: 99

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

| DEPOSITANTE           | TIPO PAGO    | BANCO           | CUENTA    | No. PAGO | FECHA PGO  | Vr. PAGO      |
|-----------------------|--------------|-----------------|-----------|----------|------------|---------------|
| BRIGARD & CASTRO LTDA | CONSIGNACION | BANCO DE BOGOTA | 062754387 | 79585914 | 06/11/2008 | 31,842,000.00 |

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

| CANT. | RENTISTICO  | CONCEPTO                             | TOTAL CONCEPTO |
|-------|-------------|--------------------------------------|----------------|
| 1     | 50005-01-09 | OTROS SERVICIOS DE PROPIEDAD I       |                |
|       |             | 54 INFORMACION DETALLADA DE UN TRAMI | 23,000.00      |
|       |             | TOTAL :                              | \$ 23,000.00   |

ON: VEINTITRES MIL PESOS

RESPONSABLE : \_\_\_\_\_

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. \_\_\_\_\_

109 339

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 09 - 1,221  
FECHA : ENERO 6 DE 2009

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 09-008313- -00000-0000

Fecha: 2009-01-29 16:34:09 Dep. 2020 NUECREACIONE  
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII  
Act. 411 PRESENTACION Folios: 99

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

| DEPOSITANTE           | TIPO PAGO      | BANCO | CUENTA | No. PAGO | FECHA PGO  | Vr. PAGO     |
|-----------------------|----------------|-------|--------|----------|------------|--------------|
| BRIGARD & CASTRO LTDA | RECIBO DE CAJA |       |        | 1039     | 06/01/2009 | 5,012,000.00 |

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

| CANT. | RENTISTICO  | CONCEPTO                       | TOTAL CONCEPTO                        |
|-------|-------------|--------------------------------|---------------------------------------|
| 1     | 50005-01-09 | OTROS SERVICIOS DE PROPIEDAD I | 998 VALOR COMPLEMENTO TARIFA A#0 ANTR |
|       |             | TOTAL :                        | \$ 2,000.00                           |

SON: DOS MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No.

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

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
12 June 2008 (12.06.2008)

PCT

(10) International Publication Number  
WO 2008/068770 A3

- (51) International Patent Classification:  
A61K 31/277 (2006.01) A61K 31/167 (2006.01)  
A61K 31/10 (2006.01)
- (21) International Application Number:  
PCT/IN2007/000274
- (22) International Filing Date: 5 July 2007 (05.07.2007)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:  
1074/MUM/2006 7 July 2006 (07.07.2006) IN
- (71) Applicant (for all designated States except US):  
PANACEA BIOTEC LIMITED [IN/IN]; 201, Samarpan  
Complex, New-Link Road, Chakala, Andheri(E), Mumbai  
400 099, Maharashtra (IN).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): SINGH, Amar-  
jit [IN/IN]; 201, Samarpan Complex, New-Link Road,  
Chakala, Andheri(E), Mumbai 400 099, Maharashtra  
(IN). SINGH, Sarabjit [IN/IN]; 201, Samarpan Complex,  
New-Link Road, Chakala, Andheri(E), Mumbai 400 099,  
Maharashtra (IN). PUTHLI, Shivanand [IN/IN]; 201,  
Samarpan Complex, New-Link Road, Chakala, And-  
heri(E), Mumbai 400 099, Maharashtra (IN).
- (74) Agent: ANDHERIA, Mahalaxmi; Panacea Biotec Lim-  
ited, 201, Samarpan Complex, New-Link Road, Chakala,  
Andheri(E), Mumbai 400 099, Maharashtra (IN).

- (81) Designated States (unless otherwise indicated, for every  
kind of national protection available): AE, AG, AL, AM,  
AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH,  
CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG,  
ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL,  
IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK,  
LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW,  
MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL,  
PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY,  
TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA,  
ZM, ZW.
- (84) Designated States (unless otherwise indicated, for every  
kind of regional protection available): ARIPO (BW, GH,  
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,  
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),  
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,  
FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL,  
PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM,  
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))
- of inventorship (Rule 4.17(iv))

Published:

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

- (88) Date of publication of the international search report:  
16 October 2008

(54) Title: PHARMACEUTICAL COMPOSITION CONTAINING BICALUTAMIDE AND A METHOD FOR ITS USE

(57) Abstract: The invention refers to an oral bicalutamide-containing formulation with a modified release pattern. The composition is suitable for being administered in a twice-a-week, twice-a-week and once-a-week dosing schedule. The composition is used for producing an anti-androgenic effect.

WO 2008/068770 A3

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/IN 2007/000274

## A. CLASSIFICATION OF SUBJECT MATTER

IPC<sup>8</sup>: **A61K 31/277** (2006.01); **A61K 31/10** (2006.01); **A61K 31/167** (2006.01)

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<sup>8</sup>: A61K

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

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

EPODOC

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages                                                                 | Relevant to claim No. |
|-----------|----------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|
| X         | WO 2004/100944 A1 (SYNTHON B.V.) 25 November 2004<br>(25.11.2004)<br><i>examples; claims 1,4,6,7</i>                                               | 20,21                 |
| X         | JP 2005/060302 A (SUMITOMO CHEMICAL CO)<br>10 March 2005 (10.03.2005)<br><i>abstract; online-translation of the JPO, claims 1,2</i>                | 20-22                 |
| PX        | WO 2006/076533 A1 (ELAN PHARMA INTERNATIONAL LIMITED) 20 July 2006 (20.07.2006)<br><i>page 7, lines 8-9; pages 17-20, line 2; claims 1,2,19-22</i> | 20-22                 |

☐ Further documents are listed in the continuation of Box C.☒ See patent family 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 application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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

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

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

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

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&amp;" document member of the same patent family

Date of the actual completion of the international search  
22 July 2008 (22.07.2008)Date of mailing of the international search report  
11 August 2008 (11.08.2008)Name and mailing address of the ISA/ AT  
**Austrian Patent Office**  
Dresdner Straße 87, A-1200 ViennaAuthorized officer  
**KRENN M.**

Facsimile No. +43 / 1 / 534 24 / 535

Telephone No. +43 / 1 / 534 24 / 435

**INTERNATIONAL SEARCH REPORT**

International application No.  
PCT/IN 2007/000274

**Continuation of first sheet**

**Continuation No. II:**

**Observations where certain claims were found unsearchable**

**(Continuation of item 2 of first sheet)**

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

Claims Nos.: 1-19,23,24 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:

Claims 1-6 refer to a method of treatment of the human/animal body by therapy, for which a search directed to the alleged effect is usually carried out. However, as the concerned claims do not disclose any concrete information about how the trice-a-week dosing, twice-a-week dosing resp. once-a-week dosing is realized, the claimed method for production of an anti-androgenic effect remains a mere wishful notion.

Claims 7-19 are incomplete, because a modified release can only be achieved, if appropriate adjuvants such as polymers or coatings are used. Said components responsible for the modified release should be specified. Furthermore, it should be stated that a mode of administration is not an appropriate feature for characterization of a product claim. It is further insufficient to characterize a product via its dissolution profile (claims 23,24).

INTERNATIONAL SEARCH REPORT  
Information on patent family members

International application No.  
PCT/IN 2007/000274

| Patent document cited<br>in search report |   |            | Publication<br>date |  | Patent family<br>member(s) | Publication<br>date |  |
|-------------------------------------------|---|------------|---------------------|--|----------------------------|---------------------|--|
| WO                                        | A | 2004100944 |                     |  | FI U1 7526U                | 2007-06-12          |  |
|                                           |   |            |                     |  | JP T 2006528221T           | 2006-12-14          |  |
|                                           |   |            |                     |  | NO A 20055943              | 2006-01-25          |  |
|                                           |   |            |                     |  | EP A1 1622604              | 2006-02-08          |  |
|                                           |   |            |                     |  | CA A1 2525318              | 2004-11-25          |  |
|                                           |   |            |                     |  | AU A1 2004238038           | 2004-11-25          |  |
| JP                                        | A | 2005060302 |                     |  | WO A1 2005014531           | 2005-02-17          |  |
|                                           |   |            |                     |  | JP A 2005060302            | 2005-03-10          |  |
| WO                                        | A | 2006076533 |                     |  | US A1 2006269596           | 2006-11-30          |  |
|                                           |   |            |                     |  | WO A1 2006076533           | 2006-07-20          |  |

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
12 June 2008 (12.06.2008)

PCT

(10) International Publication Number  
**WO 2008/068770 A2**

(51) International Patent Classification:

A61K 31/167 (2006.01) A61K 9/20 (2006.01)  
A61K 31/10 (2006.01)

(21) International Application Number:

PCT/IN2007/000274

(22) International Filing Date: 5 July 2007 (05.07.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

1074/MUM/2006 7 July 2006 (07.07.2006) IN

(71) Applicant (for all designated States except US):  
**PANACEA BIOTEC LIMITED** [IN/IN]; 201, Samarpan  
Complex, New-Link Road, Chakala, Andheri(E), Mumbai  
400 099, Maharashtra (IN).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **SINGH, Amar-  
jit** [IN/IN]; 201, Samarpan Complex, New-Link Road,  
Chakala, Andheri(E), Mumbai 400 099, Maharashtra  
(IN). **SINGH, Sarabjit** [IN/IN]; 201, Samarpan Complex,  
New-Link Road, Chakala, Andheri(E), Mumbai 400 099,  
Maharashtra (IN). **PUTHLI, Shivanand** [IN/IN]; 201,  
Samarpan Complex, New-Link Road, Chakala, And-  
heri(E), Mumbai 400 099, Maharashtra (IN).

(74) Agent: **ANDHERIA, Mahalaxmi**; Panacea Biotec Lim-  
ited, 201, Samarpan Complex, New-Link Road, Chakala,  
Andheri(E), Mumbai 400 099, Maharashtra (IN).

(81) Designated States (unless otherwise indicated, for every  
kind of national protection available): AE, AG, AL, AM,  
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- as to applicant's entitlement to apply for and be granted a  
patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the  
earlier application (Rule 4.17(iii))
- of inventorship (Rule 4.17(iv))

**Published:**

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

(54) Title: METHODS AND COMPOSITIONS FOR PRODUCING ANTI-ANDROGENIC EFFECTS

(57) Abstract: The invention provides a method and a composition for producing an anti-androgenic effect in a mammal. The method comprises administering a modified release pharmaceutical composition of bicalutamide to a mammal, with a reduced dosing frequency, for improved patient convenience and compliance. The composition of the invention also provides for a higher bioavailability and improved pharmacokinetic profile as compared to a conventional bicalutamide composition.

WO 2008/068770 A2

**METHODS AND COMPOSITIONS FOR PRODUCING ANTI-ANDROGENIC EFFECTS**

**FIELD OF THE INVENTION**

5 This invention belongs to the field of pharmaceutical science. It relates to methods and compositions of bicalutamide, a non-steroidal anti-androgen compound.

**BACKGROUND OF THE INVENTION**

10 Androgens are natural or synthetic compounds, usually steroid hormones, which stimulate and control the development and maintenance of masculine characteristics by binding to androgen receptors. Being anabolic steroids, they are known to stimulate growth of certain tissues like the prostate and other peripheral tissues, including primary or metastatic prostate tumor cells. Androgens like testosterone and dihydrotestosterone exert their influence on cell functions by binding to androgen receptors. The high response rate to first line 'Androgen deprivation therapy' and the presence of androgen receptors in both primary and metastatic prostate tumor cells support the idea that the receptor is an important mediator of prostate cancer development and growth.

20 Prostatic carcinomas are androgen dependent; hence various treatment strategies focus on negating the role of androgens (i.e., testosterone and dihydrotestosterone) in prostate tumor growth. These treatment strategies include use of luteinizing hormone-releasing hormone ("LHRH") analogues to suppress testicular androgen production (chemical castration) or orchiectomy (surgical castration) to eliminate androgen production.

25 In recent years, a class of drugs, known as anti-androgens, has widely been used for the treatment of prostate cancer. The biologic activity of androgens is mediated through the formation of a non-covalent androgen receptor-steroid complex. Anti-androgens inhibit formation of this complex and, thus, negate the role of endogenous steroids in androgen-dependent growth of the prostate.

30 Combinations of the above mentioned strategies have also been studied in a number of cases to evaluate the relative efficacies and survival benefits. A combination of anti-androgen drugs with castration (either chemical or surgical), not only prevents the action of testosterone produced by the testes but also the small, but important amount which is produced by other glands i.e. the adrenal glands. Such therapy is sometimes called Complete or Maximal Androgen Blockade

35

(CAB or MAB). In advanced disease a combination of an LHRH analogue (e.g. goserelin, leuprolide) (generally administered as long acting injectable implants or depots) and a non-steroidal anti-androgen (e.g. bicalutamide, given as oral tablets) can be used. Clinical trials identify that men treated with such combination therapy may live longer than those treated with an LHRH analogue alone. Combination therapy may sometimes also be used prior to surgery or radiotherapy (neoadjuvant) to reduce the size of the tumour.

Bicalutamide, an acylanilide, is a non-steroidal anti-androgen, is a 'second generation' anti-androgen, which has more advantageous properties than the other known anti-androgens, like Flutamide or Nilutamide. (For example, refer to Schellhammer PF et al., *Urology*, 50: 330-6, (1997); and to McLeod DG, *Oncologist*, 2:18-27, (1997).) The commercially available product by AstraZeneca is CASODEX<sup>(TM)</sup> and its chemical formula is 4-cyano-3-trifluoromethyl-N-(3-p-fluorophenylsulphonyl-2-hydroxy-2-methylpropionyl) aniline. The compound has been disclosed in patents like United States patent No. 4636505 and European Patent No. 100172. Its anti-androgenic activity resides almost exclusively in (R) – bicalutamide, with little, if any, activity in (S) – bicalutamide. It is used at a dosage of 50mg once daily in combination with a luteinising hormone-releasing hormone analogue or surgical castration for the treatment of advanced prostate cancer. It is also given at a dosage of 150 mg once daily as monotherapy for the treatment of early (localized or locally advanced) non-metastatic prostate cancer. It has a long half life of approximately 5.8 days and time to peak plasma concentration of about 31 hours.

Reports on bicalutamide detail that after daily administration of bicalutamide to patients the relationship between steady state concentration (C<sub>ss</sub>) and dose is linear only between 10 and 50mg/day, it shows departure from linearity at doses between 100 and 200 mg per day and increased departure from linearity at 300mg/day. Above 300 mg, especially when studied at 450 and 600mg dose, no further increase in C<sub>ss</sub> is observed. This non-linearity and plateau in C<sub>ss</sub> at higher dose has been attributed to decreased drug absorption and saturable transport across GI tract. Refer to Tyrell CJ et al., *Eur Urol* 33:39-53, (1998).

Prostate cancer most often advances very slowly and many patients often have no symptoms, particularly in the early stages. Most men with prostate cancer will live with their disease for many years. Hence it is important to consider their choice when faced with the androgen deprivation therapies mentioned above. For example, refer to Nyman, et al., *BJU International*, 96: 1014 – 1018, (2005), where a Swedish study in 150 patients was conducted to investigate

their choice amongst the three androgen deprivation therapies: bicalutamide, GnRH analogue and orchiectomy. Most men preferred oral tablets of anti-androgen bicalutamide, but they also indicated dissatisfaction; one of the main reasons for which was the need to take the drug daily. Bicalutamide is often used for months to years together. Hence, in such situations, it becomes  
5 difficult to take medications daily and there is need for a therapy which reduces the dosing frequency, thereby increasing patient comfort and compliance.

United States Application No. 2004067257 discloses solid dispersions of bicalutamide with enteric polymers having a pKa of 3 to 6 for increasing the bioavailability of the drug, for  
10 reducing inter-patient variability in plasma concentrations of bicalutamide; or for treating and/or reducing the risk of prostate cancer in a patient. The patient has to take the pharmaceutical dose daily.

International Publication WO2006069098 discloses nanoparticulate bicalutamide formulations,  
15 having bicalutamide particles with an effective average particle size of less than about 2000 nm and containing surface stabilizers, which target an increase in the bioavailability of the drug. The publication teaches compositions that can be formulated for parenteral injection (e. g., intravenous, intramuscular, or subcutaneous), oral administration in solid, liquid, or aerosol form, vaginal, nasal, rectal, ocular, local (powders, ointments or drops), buccal, intracisternal,  
20 intraperitoneal, or topical administration, and the like. The invention relates to increasing the solubility and bioavailability of bicalutamide.

International Publication WO2006076533 discloses controlled release compositions of acylanilide particles, particularly bicalutamide, for use in combination therapy and which are  
25 purported to deliver the active ingredient in a pulsed or bi-modal manner on oral administration. The compositions are multiparticulate where the subsequent pulses are obtained by coating the population of particles. No details of formulation or any examples are given. The compositions are meant for once daily administration.

30 International Publication WO2006090129 relates to a method for treating metastatic prostate cancer by administering bicalutamide formulations which deliver mean steady state plasma levels of R-bicalutamide of at least 40 ug/ml. Examples given in the application are mostly related to solid dispersions and R-bicalutamide formulations, meant to be given daily.

Some attempts have been made earlier to improve the absorption and bioavailability of bicalutamide at higher doses but still there is a need to develop and provide a composition of bicalutamide that can overcome the saturable absorption and provide a linear relationship between steady state concentration and dosage over a wide dose range of from about 50 to about 600mg.

It is also desirable to have a method for producing an anti-androgenic effect in a mammal by providing bicalutamide with a reduced dosing frequency and maintaining its therapeutically effective levels for a prolonged period of time. For such a method, although the dose administered during a dosing interval may be same or lesser as compared to the total dose given during the interval by conventional once-daily therapy, the method utilizes a higher one-time dose as compared to a conventional once-daily dose. This dose may be 150mg or higher i.e. higher than the once-daily unit dose. However, as is known, for high doses, bicalutamide exhibits non-linear kinetics, possibly due to its saturable absorption. (Also, refer to Kolvenbag et al., *Prostate*, 34:61-72, (1998). Hence, inclusion of such doses may result in incomplete absorption, leading to sub-optimal drug levels in the plasma. Furthermore, at higher doses, high inter-patient variability in the pharmacokinetics of bicalutamide has been reported.

Therefore, there is a need in the art for a method for producing an anti-androgenic effect in a mammal in need thereof which solves the above and other problems.

**BRIEF DESCRIPTION OF THE INVENTION**

The inventors have now found that contrary to the expected saturation in bicalutamide absorption, it is possible to administer bicalutamide at higher doses such that therapeutically effective plasma levels of the drug are maintained in the body for a prolonged period of time.

The method and composition of the present invention provide for maintenance of therapeutically effective plasma level of bicalutamide for a prolonged period of time, and hence allow for a reduced dosing frequency.

An aspect of the present invention relates to a method for producing an anti-androgenic effect in a mammal in need thereof by oral administration of a pharmaceutically effective amount of bicalutamide with a reduced dosing frequency, such as thrice-a-week dosing, twice-a-week dosing and once-a-week dosing.

Another aspect of the present invention relates to a method for producing an anti-androgenic effect in a mammal by orally administering to the mammal a modified release pharmaceutical composition of bicalutamide in a once-a-week dosing schedule.

- 5 The present invention provides a once-a-week composition containing bicalutamide for producing an anti androgenic effect in a mammal.

- 10 An aspect of the present invention also relates to a pharmaceutically effective amount of bicalutamide which ranges from about 50mg to about 1000mg and which will be effective for the method of the invention.

- 15 Another aspect of the present invention relates to a modified release pharmaceutical composition of bicalutamide which exhibits higher bioavailability and improved pharmacokinetic profile of bicalutamide. The composition is an oral pulsed release composition wherein part of the dose of bicalutamide is released substantially immediately upon administration and the remaining part of the dose is released after a pre-determined time interval. The immediate release portion is formulated in the form of at least one uncoated or film coated tablet and the delayed release portion is formulated in the form of at least one tablet coated with delayed release polymers.

## 20 DESCRIPTION OF THE DRAWINGS

**FIG 1** shows the predicted plasma concentration time profiles of the Test and Reference bicalutamide compositions at steady state levels, in comparison with the predicted reference of 50mg bicalutamide administered daily.

- 25 **FIG 2** shows the dissolution profile of an illustrative composition of bicalutamide ("Test") from Example 3.

## DESCRIPTION OF THE INVENTION

- 30 The present invention relates to a method, preferably an oral method, for producing an anti-androgenic effect in a mammal in need thereof.

The method is provided by orally administering to a mammal, a modified release pharmaceutical composition of bicalutamide, which is administered in a thrice-a-week, twice-a-week or once-a-week dosing schedule.

Preferably, the modified release pharmaceutical composition of bicalutamide is administered in a once-a-week dosing schedule.

5 The method of the invention provides for prolonged maintenance of therapeutically effective plasma levels of bicalutamide in the body. The dosing frequency is reduced by providing a modified release pharmaceutical composition that reduces bicalutamide losses due to saturation of absorption mechanisms. Moreover, the method of the present invention provides for improved patient compliance since the inconvenience of daily dosing is avoided. The method may also provide for reduced inter-patient variability.

10

The term 'bicalutamide' as used herein contemplates all forms of bicalutamide, such as the free base, any pharmaceutically acceptable salts, esters, solvates thereof as well as the racemate, the individual isomers R-bicalutamide and S-bicalutamide and their pharmaceutically acceptable salts, esters and solvates. Accordingly, bicalutamide is used in the pharmaceutical composition of the present invention in the range of amounts equivalent to about 50mg to about 1000mg of bicalutamide.

15

'Thrice-a-week' dosing schedule as used herein, means that a dose of bicalutamide is administered three times in a week i.e. three times during a seven day period, preferably on the same three days of each weekly period.

20

'Twice-a-week' dosing schedule as used herein, means that a dose of bicalutamide is administered two times in a week i.e. two times during a seven day period, preferably on the same two days of each weekly period.

25

The term 'once-a-week' dosing schedule as used herein means that a dose of bicalutamide is administered once in a week i.e. one time during a seven day period, preferably on the same day of each week.

30

The term 'pharmaceutically effective amount' of bicalutamide as used herein indicates an amount of bicalutamide necessary to be administered to a mammal to achieve a desired therapeutic result, especially an anti-androgenic effect. The dose utilized for the above purpose will generally be from about 50mg to about 1000mg.

20  
'Reduced dosing frequency' as used herein means that the frequency of administration of bicalutamide to a mammal is less than once in a day. Thus, for example, the frequency may be thrice in a week, twice in a week or once in a week.

- 5 The method of the present invention is generally applicable to a mammal in need of anti-androgen therapy. Preferably the mammal is a human patient, more preferably male, and particularly a male who has been identified as suffering from proliferative disorders, such as prostate cancer, benign prostate hyperplasia or possibly any other genito-urinary cancers.
- 10 An aspect of the method of the present invention contemplates administering the bicalutamide composition of the present invention alone as well as in combination with other pharmaceutical agents such as anti-estrogens, for example tamoxifen; aromatase inhibitors, for example anastrozole; LH-RH analogues, for example goserelin; cytotoxic agents, such as cyclophosphamide; and any other suitable agents. The composition may also be administered as
- 15 an adjunct with orchiectomy.

Another aspect of the method of the present invention contemplates administration of one or more loading doses of bicalutamide, followed by administration of the composition of the invention as a maintenance therapy. This will allow for rapid attainment of steady state levels

20 followed by their maintenance over the period of therapy.

The composition of the invention is administered as a unit dosage and the unit dose may range from about 50mg to about 1000mg of bicalutamide. Preferably it varies from about 150mg to about 600mg and more preferably from about 150mg to about 400mg of bicalutamide

25 administered in a thrice-a-week, twice-a-week or once-a-week dosing schedule.

The modified release pharmaceutical composition of the present invention comprises of bicalutamide and suitable excipients. The composition may demonstrate any type of modified release profile which would allow for a reduced dosing frequency. Thus the modified release

30 profile according to the invention may be a controlled release, sustained release, extended release, delayed release, pulsed release, dual release, timed release, site-specific release and others, including any combinations thereof.

In one embodiment of the invention, the composition is in the form of an oral delayed release

35 product, wherein upon administration, the entire dose of bicalutamide is released after a pre-

determined time interval, in the later part of the gastro-intestinal tract. The release may be either 'all-at-once' or in a sustained manner.

5 In an embodiment of the invention, the composition is in the form of an oral pulsed release product, wherein part of the dose of bicalutamide is released substantially immediately upon administration and the remaining part of the dose is released after a pre-determined time interval.

10 In another embodiment of the invention, the composition is in the form of an oral pulsed release product, wherein part of the dose of bicalutamide is released substantially immediately upon administration and the remaining dose is released in a sustained manner after a pre-determined time interval.

15 The composition of the above embodiments may include various pharmaceutically acceptable excipients, for example, diluents such as microcrystalline cellulose, lactose, sucrose, calcium phosphates; disintegrants such as starch, cellulose derivatives, gums, crosslinked polymers and the like; binders such as starch, gelatin, sugars, cellulose derivatives, polyvinyl pyrrolidone and the like; lubricants such as talc, magnesium stearate, colloidal silicon dioxide, polyethylene glycol and mixtures thereof.

20 The composition can be formulated in the form of granules, tablets, layered tablets, mini-tablets and pellets or as capsules filled with powder, pellets, mini-tablets and/or tablets. The processes for the preparation of these compositions are well known to a person skilled in the art, and are included herein by reference.

25 In an embodiment, bicalutamide and suitable excipients are formulated together in the form of granules. The granules are compressed to form mini-tablets of bicalutamide. They may optionally be film-coated. These mini-tablets release bicalutamide substantially immediately on administration of the composition. The mini-tablets are then coated with suitable polymers  
30 which modify the release rate and time of bicalutamide. These polymers generally belong to categories such as celluloses, vinyl pyrrolidone polymers, alkylene oxide homopolymers, superdisintegrant polymers, acrylic acid polymers and gums of plant, animal, mineral or synthetic origin.

Preferably, the polymers delay the release of bicalutamide until a predetermined time interval. Preferred for the purpose are enteric polymers such as esters of cellulose and its derivatives, vinyl polymers and copolymers, pH-sensitive methacrylic acid copolymers, shellac etc. A few examples which can be used in the compositions of the invention are cellulose acetate phthalate, cellulose acetate succinate, methylcellulose phthalate, ethylhydroxycellulose phthalate, polyvinylacetatephthalate, polyvinylbutyrate acetate, vinyl acetate-maleic anhydride copolymer, styrene-maleic mono-ester copolymer, methyl acrylate-methacrylic acid copolymer, methacrylate-methacrylic acid-octyl acrylate copolymer, etc.

- 10 In an embodiment, a hard gelatin capsule is filled with the coated mini-tablets, corresponding to the total dose of bicalutamide to be administered, to form the delayed release composition of the invention.

- 15 In a preferred embodiment, a hard gelatin capsule is filled with a combination of uncoated (or film coated) and coated mini-tablets. The number of uncoated and coated mini-tablets filled depends upon the amount of bicalutamide to be released immediately and after a predetermined period of time on administration. About 80mg to about 600mg of bicalutamide is included in the uncoated mini-tablets for immediate release and about 60mg to about 400mg of bicalutamide is included in the coated mini-tablets for delayed release.

- 20 In an alternative embodiment, the composition is formulated in the form of a single tablet, consisting of a core containing bicalutamide and coated with one or more polymers which modify the release rate of the drug.

- 25 In another alternative embodiment, the composition can be formulated as a matrix composition, wherein bicalutamide and the suitable polymer are mixed together to form a matrix which modifies the release of bicalutamide.

- 30 In still another embodiment, the composition is given as part of a kit comprising agents for combination therapy. Other agents which can be included as part of the kit are anti-estrogens, for example tamoxifen; aromatase inhibitors, for example anastrozole; LH-RH analogues, for example goserelin; cytotoxic agents, such as cyclophosphamide; and any other suitable agents. In another aspect, the composition of the kit is administered daily, till a maximum of 4 weeks or till a steady state is achieved, as a loading dose, followed by weekly administration of the same composition as a maintenance dose.
- 35

23

The second aspect of the invention relates to a modified release pharmaceutical composition of bicalutamide. It has surprisingly been found that when the composition is formulated as a combination of immediate release and delayed release components in a specific manner, there is a substantial increase in the plasma levels of bicalutamide. It has also been surprisingly found that the area under the curve and the trough plasma levels for bicalutamide administered using the above composition were higher when compared with similar dose being given in conventional bicalutamide composition.

10 The composition is a solid oral composition, wherein the immediate release component is formulated as an uncoated tablet or film coated tablet which disperses to release bicalutamide substantially immediately upon oral administration. The delayed release component is formulated by coating the uncoated tablet with polymers which delay the release of bicalutamide for a predetermined time interval. The polymers are preferably enteric polymers selected from the group of esters of cellulose and its derivatives, vinyl polymers and copolymers and pH-sensitive methacrylic acid copolymers. Uncoated or film coated tablets and delayed release coated tablets are combined to form the modified release composition of the invention.

20 This composition can be used to obtain higher efficacy and better treatment of advanced, locally advanced, non-metastatic as well as metastatic prostate cancers. Dose and dosing regimen can be suitably selected depending upon the needs and disease state of the patients and depending upon whether it is given as part of combination therapy or as monotherapy.

25 An embodiment of this composition which demonstrates improved bioavailability when compared to conventional bicalutamide composition is a modified release pharmaceutical composition of bicalutamide wherein the composition is an oral pulsed release composition formulated as combination of immediate release and delayed release component comprising bicalutamide in an amount from about 20% to about 80% of the total dose in the immediate release component and in an amount from about 80% to about 20% of the total dose in the delayed release component.

35 In a specific embodiment, the modified release pharmaceutical composition when subjected to dissolution testing in USP apparatus Type I using pH change method with simulated gastric fluid of pH 1.2, buffer of pH 4.5 and simulated intestinal fluid of pH 6.8, it releases bicalutamide according to the following dissolution profile: between 20% and 65% of bicalutamide is released

in simulated gastric fluid; between 40% and 75% is released in buffer of pH 4.5; and not less than 60% is released in simulated intestinal fluid. The dissolution media comprises of 1% sodium lauryl sulphate and the composition may be tested in simulated gastric fluid for about 2 hours, in buffer of pH 4.5 for about 2 hours and in simulated intestinal fluid for the remaining period of time.

**Clinical study:**

A study in a small group of volunteers was designed to evaluate the pharmacokinetics of a single dose administration of composition of the invention and compare it with the pharmacokinetics of a similar dose of Casodex® over a period of one week.

Study design: Open-label, randomized, fasted, single dose pharmacokinetic study using parallel study design. 12 healthy human volunteers were used (6 volunteers for each group). Test composition comprised 250 mg bicalutamide and was formulated to release part of the dose immediately upon administration and part of the dose after a predetermined time interval. Reference composition was five 50 mg Casodex® tablets administered together. Blood sampling was done pre-dose and after pre-determined time intervals over one week. Pharmacokinetic parameters assessed were Cmax, Tmax, AUCt and AUCinf.

**Results:**

The pharmacokinetic data derived from the trial was as given in Table 1 below:

**Table 1:**

| Product | N Obs | Parameter         | N | Mean      |
|---------|-------|-------------------|---|-----------|
| R       | 6     | Cmax (ng/ml)      | 6 | 1774.43   |
|         |       | AUCt (ng.hr/ml)   | 6 | 201978.96 |
|         |       | AUCinf (ng.hr/ml) | 6 | 325810.62 |
| T       | 6     | Cmax (ng/ml)      | 6 | 1928.17   |
|         |       | AUCt (ng.hr/ml)   | 6 | 231661.88 |
|         |       | AUCinf (ng.hr/ml) | 6 | 489684.23 |

As seen from the table the AUCinf for the test product is about 1.5 times more than the AUCinf for the reference product indicating an improved absorption and bioavailability obtained from the composition of present invention. The increased absorption will be useful in faster buildup of steady state levels, in addition to reduced dosing/dosing frequency.

To predict and compare the kinetics of the Test and Reference compositions at steady state, the data from the trial was fed into the software Winnonlin®. The predicted plasma concentration time profiles of the Test and Reference compositions at steady state levels are shown in Figure

1.

As can be seen from the figure, the method and the composition of the invention will result in an improved plasma profile of bicalutamide as compared to the Reference product. Also, the plasma level maintained by once-a-week administration over one week may be comparable or higher than the predicted plasma level of daily administration of 50 mg reference.

Steady state pharmacokinetic parameters were predicted for the Test and Reference products at 85<sup>th</sup> day of dosing. The data is presented in the following Table 2.

Table 2:

| Parameter          | Least-Squares Means |           | Ratio | 90% Confidence Interval |       |
|--------------------|---------------------|-----------|-------|-------------------------|-------|
|                    | Test                | Reference |       | Lower                   | Upper |
| AUC 0-τ (ng-hr/mL) | 437704              | 320207    | 1.367 | 0.921                   | 1.813 |
| Cmax (ng/mL)       | 3417                | 2625      | 1.302 | 0.972                   | 1.631 |
| Cmin (ng/mL)       | 1805                | 1148      | 1.572 | 0.907                   | 2.236 |
| Tmax (hour)        | 32.8                | 27.7      | 1.184 | -                       | -     |
| T½ (hour)          | 131                 | 105       | 1.251 | -                       | -     |
| Fluctuation (%)    | 67.9                | 81.1      | 0.836 | -                       | -     |

As seen in the table 2 above for all the predicted steady state pharmacokinetic parameters, the test product has a higher value than the reference product, and the test product has less fluctuation compared to the reference product, indicating better absorption and bioavailability and an extended half life for the test product as well as a potential for reduced variability.

Various modifications of the method of the invention may be made without departing from the spirit or scope of the invention. The following non-limiting examples illustrate an embodiment of the invention and should not be construed to limit the scope of the invention.

**Example 1**

**Table 3: Formula (Core Tablet):**

| Sr. No. | Ingredient              | Qty (mg/tab) |
|---------|-------------------------|--------------|
| 1       | Bicalutamide            | 250.00       |
| 2       | Lactose monohydrate     | 188.00       |
| 3       | Sodium starch glycolate | 35.00        |
| 4       | Polyvinyl pyrrolidone   | 7.50         |
| 5       | Purified water          | q.s.         |
| 6       | Sodium starch glycolate | 17.50        |
| 7       | Magnesium stearate      | 2.00         |

**Table 4: Formula (Sub-Coat Composition):**

| Sr. No. | Ingredients                    | Qty (gms/Kg) |
|---------|--------------------------------|--------------|
| 1       | Hydroxypropyl methylcellulose  | 50.00        |
| 2       | Polyethylene Glycol (PEG 6000) | 7.50         |
| 3       | Methanol                       | 628.30       |
| 4       | Dichloromethane                | 314.20       |

**Table 5: Formula (Enteric Coat Composition):**

| Sr. No. | Ingredients                                                                          | Qty (gms/Kg) |
|---------|--------------------------------------------------------------------------------------|--------------|
| 1       | Methacrylic acid co-polymer (Methacrylic Acid - Methyl Methacrylate Copolymer (1:2)) | 53.85        |
| 2       | Methacrylic acid co-polymer (Methacrylic Acid - Methyl Methacrylate Copolymer (1:1)) | 23.07        |
| 3       | Triethyl citrate                                                                     | 15.38        |
| 4       | Acetone                                                                              | 276.92       |
| 5       | Isopropyl alcohol                                                                    | 553.07       |
| 6       | Purified water                                                                       | 39.23        |
| 7       | Talc                                                                                 | 38.46        |

Bicalutamide, Sodium starch glycolate (intra-granular portion) and lactose monohydrate were sifted and blended in the amounts mentioned in the Table 2 above. Polyvinyl pyrrolidone dissolved in sufficient quantity of purified water was used to granulate the dry powder blend.

The blend was dried and sieved to obtain dry granules. The granules were then blended with the remaining amount of sodium starch glycolate and magnesium stearate. The lubricated blend was compressed into tablets using round punches.

The sub-coating solution was prepared by dissolving PEG 6000 and Hydroxypropyl Methyl Cellulose in the mixture of methanol and dichloromethane. The tablets were coated using the above solution, till a tablet weight gain of about 2-3 % w/w was achieved.

The enteric coating dispersion was prepared by mixing acetone, isopropanol and purified water, and dispersing the methacrylic acid co-polymers, talc and triethyl citrate in them. The sub-coated tablets were coated with the above solution till a weight gain of 10-11% w/w was achieved.

Example 2

Table 6: Formula (Core Tablet):

| Sr. No. | Ingredient              | Qty (mg/tab) |
|---------|-------------------------|--------------|
| 1       | Bicalutamide            | 50.00        |
| 2       | Lactose monohydrate     | 37.60        |
| 3       | Sodium starch glycolate | 7.00         |
| 4       | Polyvinyl pyrrolidone   | 1.50         |
| 5       | Purified water          | q.s.         |
| 6       | Sodium starch glycolate | 3.50         |
| 7       | Magnesium stearate      | 0.40         |

Table 7: Formula (Sub-Coat Composition):

| Sr. No. | Ingredients                    | Qty (gms/Kg) |
|---------|--------------------------------|--------------|
| 1       | Hydroxypropyl methylcellulose  | 50.00        |
| 2       | Polyethylene Glycol (PEG 6000) | 7.50         |
| 3       | Methanol                       | 628.30       |
| 4       | Dichloromethane                | 314.20       |

Table 8: Formula (Enteric Coat Composition):

| Sr. No. | Ingredients                                                                          | Qty (gms/Kg) |
|---------|--------------------------------------------------------------------------------------|--------------|
| 1       | Methacrylic acid co-polymer (Methacrylic Acid - Methyl Methacrylate Copolymer (1:2)) | 53.85        |
| 2       | Methacrylic acid co-polymer (Methacrylic Acid - Methyl Methacrylate Copolymer (1:1)) | 23.07        |
| 3       | Triethyl citrate                                                                     | 15.38        |
| 4       | Acetone                                                                              | 276.92       |
| 5       | Isopropyl alcohol                                                                    | 553.07       |
| 6       | Purified water                                                                       | 39.23        |
| 7       | Talc                                                                                 | 38.46        |

5 The process followed was the same as in Example 1. The tablets corresponding to a total dose of 250 mg bicalutamide (i.e. five coated tablets) were filled into empty hard gelatin capsule.

Example 3

10

Table 9: Formula (Core Tablet):

| Sr. No. | Ingredient                | Qty (mg/tab) |
|---------|---------------------------|--------------|
| 1       | Bicalutamide (Micronized) | 50.00        |
| 2       | Lactose monohydrate       | 61.00        |
| 3       | Sodium starch glycolate   | 11.20        |
| 4       | Polyvinyl pyrrolidone     | 2.40         |
| 5       | Purified water            | q.s.         |
| 6       | Sodium starch glycolate   | 4.60         |
| 7       | Magnesium stearate        | 0.60         |

Table 10 : Formula (Sub-Coat Composition):

| Sr. No. | Ingredients                          | Qty (gms/Kg) |
|---------|--------------------------------------|--------------|
| 1       | Opadry (Hypromellose coating powder) | 100          |
| 2       | Purified water q.s.                  | 900          |

15

Table 11 : Formula (Enteric Coat Composition):

| Sr. No. | Ingredients                                                                          | Qty (gms/Kg) |
|---------|--------------------------------------------------------------------------------------|--------------|
| 1       | Methacrylic acid co-polymer (Methacrylic Acid - Methyl Methacrylate Copolymer (1:2)) | 53.850       |
| 2       | Methacrylic acid co-polymer (Methacrylic Acid - Methyl Methacrylate Copolymer (1:1)) | 23.078       |
| 3       | Triethyl citrate                                                                     | 15.386       |
| 4       | Acetone                                                                              | 276.920      |
| 5       | Isopropyl alcohol                                                                    | 553.077      |
| 6       | Purified water                                                                       | 39.230       |
| 7       | Talc                                                                                 | 38.460       |

The process followed was the same as in Example 1. Three uncoated tablets, corresponding to a total dose of 150mg and two coated tablets, corresponding to a total dose of 100mg were filled into a hard gelatin capsule. The composition was subjected to a dissolution study using pH change method using buffers of pH 1.2, 4.5, and 6.8 with 1% Sodium Lauryl Sulphate (SLS). The study was carried out in USP apparatus Type I. The dissolution profile obtained is indicated in Figure 2.

Example 4

Table 12: Formula (Core Tablet):

| Sr. No. | Ingredient              | Qty (mg/tab) |
|---------|-------------------------|--------------|
| 1       | Bicalutamide            | 350.00       |
| 2       | Lactose monohydrate     | 199.60       |
| 3       | Polyvinyl pyrrolidone   | 18.00        |
| 4       | Sodium starch glycolate | 30.00        |
| 5       | Magnesium stearate      | 2.40         |

Table 13: Formula (Sub-Coat Composition):

| Sr. No. | Ingredients                   | Qty (gms/Kg) |
|---------|-------------------------------|--------------|
| 1       | Hydroxypropyl methylcellulose | 50.00        |
| 2       | Polyethylene Glycol           | 7.50         |
| 3       | Methanol                      | 628.30       |
| 4       | Dichloromethane               | 314.20       |

Table 14: Formula (Enteric Coat Composition):

| Sr. No. | Ingredients                                                                          | Qty (gms/Kg) |
|---------|--------------------------------------------------------------------------------------|--------------|
| 1       | Methacrylic acid co-polymer (Methacrylic Acid - Methyl Methacrylate Copolymer (1:2)) | 80.00        |
| 2       | Methacrylic acid co-polymer (Methacrylic Acid - Methyl Methacrylate Copolymer (1:1)) | 6.4          |
| 3       | Triethyl citrate                                                                     | 16.80        |
| 4       | Acetone                                                                              | 297.90       |
| 5       | Isopropyl alcohol                                                                    | 515.60       |
| 6       | Purified water                                                                       | 42.40        |
| 7       | Talc                                                                                 | 43.20        |

The process of manufacturing was similar to that in Example 1.

Example 5

Table 15: Formula (Core Tablet):

| Sr. No. | Ingredient              | Qty (mg/tab) |
|---------|-------------------------|--------------|
| 1       | Bicalutamide            | 70.00        |
| 2       | Lactose monohydrate     | 39.92        |
| 3       | Polyvinyl pyrrolidone   | 3.60         |
| 4       | Sodium starch glycolate | 6.00         |
| 5       | Magnesium stearate      | 0.48         |

Table 16: Formula (Sub-Coat Composition):

| Sr. No. | Ingredients                   | Qty (gms/Kg) |
|---------|-------------------------------|--------------|
| 1       | Hydroxypropyl methylcellulose | 50.00        |
| 2       | Polyethylene Glycol           | 7.50         |
| 3       | Methanol                      | 628.30       |
| 4       | Dichloromethane               | 314.20       |

Table 17: Formula (Enteric Coat Composition):

| Sr. No. | Ingredients                                                                          | Qty (gms/Kg) |
|---------|--------------------------------------------------------------------------------------|--------------|
| 1       | Methacrylic acid co-polymer (Methacrylic Acid - Methyl Methacrylate Copolymer (1:2)) | 80.00        |
| 2       | Methacrylic acid co-polymer (Methacrylic Acid - Methyl Methacrylate Copolymer (1:1)) | 6.4          |
| 3       | Triethyl citrate                                                                     | 16.80        |
| 4       | Acetone                                                                              | 297.90       |
| 5       | Isopropyl alcohol                                                                    | 515.60       |
| 6       | Purified water                                                                       | 42.40        |
| 7       | Talc                                                                                 | 43.20        |

The formula and process was similar to that in Example 1. The tablets corresponding to a total dose of 350 mg bicalutamide (i.e. five coated tablets) were filled into empty hard gelatin capsule shells.

Example 6

Table 18: Formula (Core Tablet):

| Sr. No. | Ingredient                    | Qty (mg/tab) |
|---------|-------------------------------|--------------|
| 1       | Bicalutamide                  | 50.00        |
| 2       | Microcrystalline cellulose    | 36.10        |
| 3       | Hydroxypropyl methylcellulose | 60.00        |
| 4       | Sodium starch glycolate       | 3.50         |
| 5       | Magnesium stearate            | 0.40         |

Table 19: Formula (Sub-Coat Composition):

| Sr. No. | Ingredients                   | Qty (gms/Kg) |
|---------|-------------------------------|--------------|
| 1       | Hydroxypropyl methylcellulose | 50.00        |
| 2       | Polyethylene Glycol           | 7.50         |
| 3       | Methanol                      | 628.30       |
| 4       | Dichloromethane               | 314.20       |

Table 20: Formula (Enteric Coat Composition):

| Sr. No. | Ingredients                                                                          | Qty (gms/Kg) |
|---------|--------------------------------------------------------------------------------------|--------------|
| 1       | Methacrylic acid co-polymer (Methacrylic Acid - Methyl Methacrylate Copolymer (1:2)) | 80.00        |
| 2       | Methacrylic acid co-polymer (Methacrylic Acid - Methyl Methacrylate Copolymer (1:1)) | 6.4          |
| 3       | Triethyl citrate                                                                     | 16.80        |
| 4       | Acetone                                                                              | 297.90       |
| 5       | Isopropyl alcohol                                                                    | 515.60       |
| 6       | Purified water                                                                       | 42.40        |
| 7       | Talc                                                                                 | 43.20        |

Bicalutamide, microcrystalline cellulose, and Hydroxypropyl methylcellulose were sifted and blended in the amounts mentioned in the Table 18 above. The mixture was further blended with sodium starch glycolate and lubricated with magnesium stearate. The lubricated blend was compressed into tablets on a rotary tablet compression machine. The tablets were sub coated and then enteric coated according to the manufacturing procedure mentioned in Example 1. The

tablets corresponding to a total dose of 250 mg bicalutamide (i.e. five coated tablets) were filled into empty hard gelatin capsule shells.

**Example 7**

**Table 21: Formula (Immediate release Tablet):**

| Sr. No. | Ingredient              | Qty (mg/tab) |
|---------|-------------------------|--------------|
| 1       | Bicalutamide            | 100.00       |
| 2       | Lactose monohydrate     | 75.20        |
| 3       | Sodium starch glycolate | 14.00        |
| 4       | Polyvinyl pyrrolidone   | 3.00         |
| 5       | Purified water          | q.s.         |
| 6       | Sodium starch glycolate | 7.00         |
| 7       | Magnesium stearate      | 0.80         |

**Table 22: Formula (Sustained release Tablet):**

| Sr. No. | Ingredient                    | Qty (mg/tab) |
|---------|-------------------------------|--------------|
| 1       | Bicalutamide                  | 250.00       |
| 2       | Microcrystalline cellulose    | 180.50       |
| 3       | Hydroxypropyl methylcellulose | 300.00       |
| 4       | Sodium starch glycolate       | 17.50        |
| 5       | Magnesium stearate            | 2.00         |

Immediate release Tablet: Bicalutamide, Sodium starch glycolate (intra-granular portion) and lactose monohydrate were sifted and blended in the amounts mentioned in the Table 20 above. Polyvinyl pyrrolidone dissolved in sufficient quantity of purified water was used to granulate the dry powder blend. The blend was dried and sieved to obtain dry granules. The granules were then blended with the remaining amount of sodium starch glycolate and magnesium stearate. The lubricated blend was compressed into tablets using 6 mm round punches.

Sustained release Tablet: Bicalutamide, microcrystalline cellulose, and Hydroxypropyl methylcellulose were sifted and blended in the amounts mentioned in the Table 22 above. The mixture was further blended with sodium starch glycolate and lubricated with magnesium stearate. The lubricated blend was compressed into tablets on a rotary tablet compression machine. The tablets were sub coated and then enteric coated according to the manufacturing procedure mentioned in Example 1. Both the tablets of the example were filled into an empty hard gelatin capsule shell.

Claims:

- 1. A method for producing an anti-androgenic effect in a mammal in need thereof comprising orally administering to the mammal a pharmaceutically effective amount of bicalutamide in a dosing schedule selected from the group of thrice-a-week dosing, twice-a-week dosing and once-a-week dosing .
- 2. The method of Claim 1, comprising orally administering to the mammal a pharmaceutically effective amount of bicalutamide in a once-a-week dosing schedule.
- 3. The method of Claim 1, wherein the pharmaceutically effective amount of bicalutamide ranges from about 150mg to about 1000mg.
- 4. A method for producing an anti-androgenic effect in a mammal in need thereof comprising orally administering to the mammal a modified release pharmaceutical composition of bicalutamide in a once-a-week dosing schedule.
- 5. The method of Claim 4, wherein the modified release pharmaceutical composition of bicalutamide is administered as a monotherapy.
- 6. The method of Claim 4, wherein the modified release pharmaceutical composition of bicalutamide is administered as part of a combination therapy.
- 7. A modified release pharmaceutical composition of bicalutamide for producing an anti-androgenic effect in a mammal in need thereof, wherein the composition is administered in a once-a-week dosing schedule.
- 8. The modified release pharmaceutical composition of Claim 7 comprising bicalutamide in the range of from about 50mg to about 1000mg.
- 9. The modified release pharmaceutical composition of Claim 8 comprising bicalutamide in the range of from about 150mg to about 600mg.
- 10. The modified release pharmaceutical composition of Claim 7 formulated in the form of granules, tablets, layered tablets, mini-tablets, pellets or capsules.

11. The modified release pharmaceutical composition of Claim 7 wherein the modified release is a controlled release, sustained release, extended release, delayed release, pulsed release, dual release, timed release or site-specific release.

5 12. The modified release pharmaceutical composition of Claim 11 wherein the modified release is delayed release or pulsed release.

10 13. The modified release pharmaceutical composition of Claim 7 wherein the composition is an oral pulsed release composition comprising at least one immediate release tablet and at least one tablet coated with delayed release polymers.

15 14. A modified release pharmaceutical composition of bicalutamide administered in a dosing schedule selected from the group of thrice-a-week dosing, twice-a-week dosing and once-a-week dosing.

15 15. A kit comprising a modified release pharmaceutical composition of bicalutamide for oral administration in a once-a-week dosing schedule.

20 16. The kit of Claim 15, wherein the modified release pharmaceutical composition is administered once daily till a maximum of four weeks, as a loading dose, followed by weekly administration of the same composition as a maintenance dose.

25 17. The kit of Claim 15, wherein the modified release pharmaceutical composition is administered once daily as a loading dose till a steady state plasma level of bicalutamide is achieved, followed by weekly administration of the same composition as a maintenance dose.

30 18. A modified release pharmaceutical composition of bicalutamide wherein the composition is an oral pulsed release composition formulated as combination of immediate release and delayed release component comprising bicalutamide in an amount from about 20% to about 80% of the total dose in the immediate release component and in an amount from about 80% to about 20% of the total dose in the delayed release component.

35 19. The modified release pharmaceutical composition of claim 18 wherein the oral pulsed release composition comprises of at least one immediate release tablet and at least one

35

tablet coated with delayed release polymers, wherein the composition demonstrates improved bioavailability as compared to a conventional bicalutamide composition.

- 5
20. A modified release pharmaceutical composition of bicalutamide having improved bioavailability, wherein the composition comprises of one or more excipients, or mixtures thereof, which extend the half life of bicalutamide.
- 10
21. The modified release pharmaceutical composition of claim 20, wherein the one or more excipients include polymers that modify the release rate and time of bicalutamide selected from the group of celluloses, vinyl pyrrolidone polymers, alkylene oxide homopolymers, superdisintegrant polymers, acrylic acid polymers and gums of plant, animal, mineral or synthetic origin.
- 15
22. The modified release pharmaceutical composition of claim 21, wherein the polymers are enteric polymers such as esters of cellulose and its derivatives, vinyl polymers and copolymers, pH-sensitive methacrylic acid copolymers, shellac and the like thereof.
- 20
23. A modified release pharmaceutical composition of bicalutamide which releases bicalutamide according to the following dissolution profile: between 20% and 65% of bicalutamide is released in simulated gastric fluid; between 40% and 75% is released in buffer of pH 4.5; and not less than 60% is released in simulated intestinal fluid; when tested in USP apparatus Type I using pH change method with simulated gastric fluid of pH 1.2, buffer of pH 4.5 and simulated intestinal fluid of pH 6.8 and wherein the dissolution media comprise of 1% sodium lauryl sulphate.
- 25
24. A modified release pharmaceutical composition of claim 23, wherein the dissolution testing is carried out in simulated gastric fluid for about 2 hours, in buffer of pH 4.5 for about 2 hours and in simulated intestinal fluid of pH 6.8 for the remaining period.
- 30

36

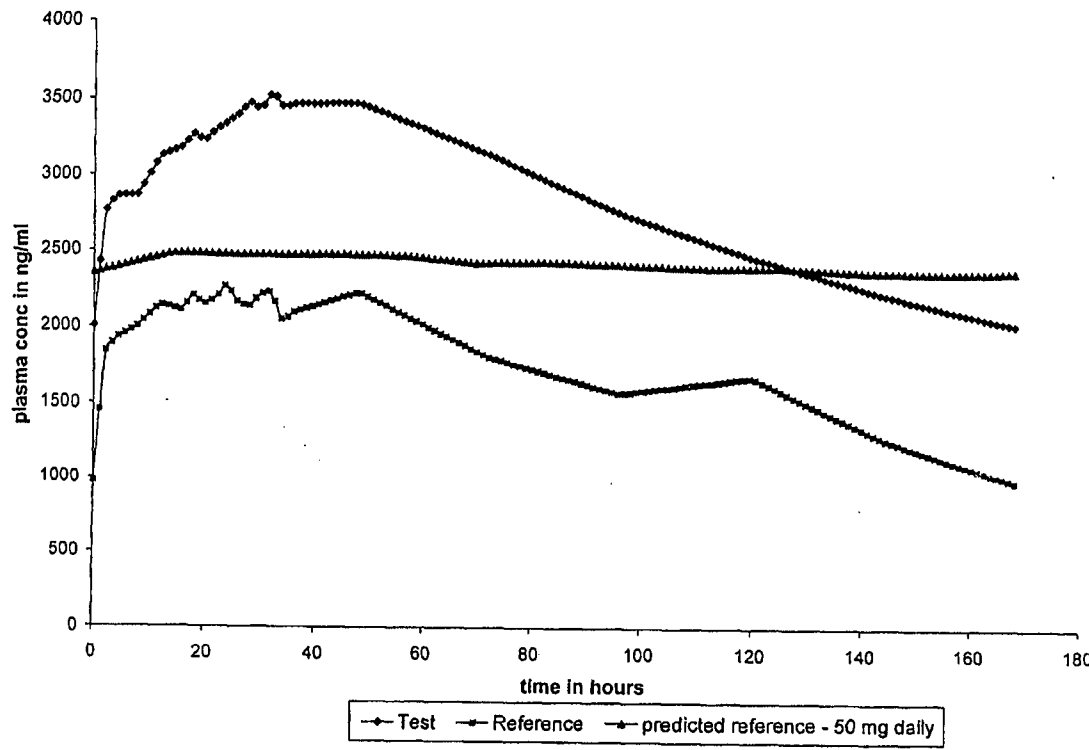


FIG 1

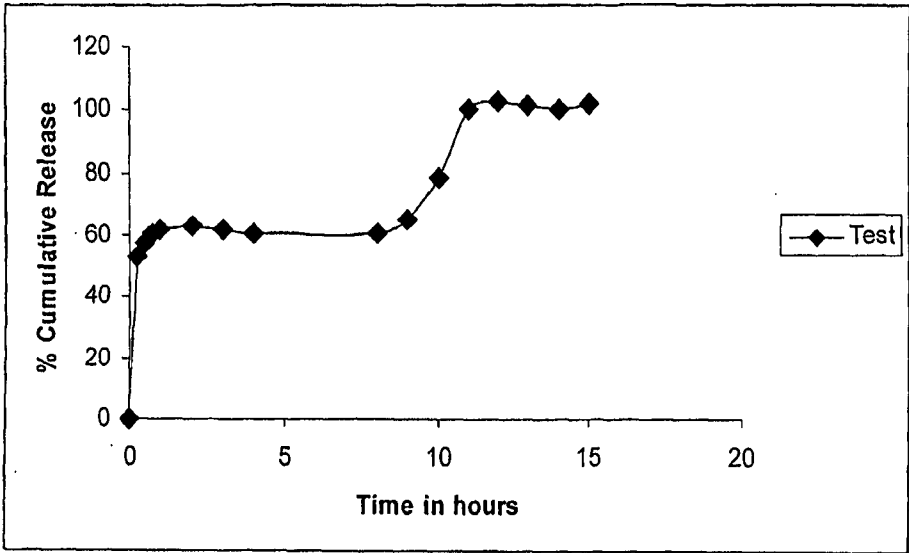


FIG 2

## (12) SOLICITUD INTERNACIONAL PUBLICADA BAJO EL TRATADO DE COOPERACIÓN DE PATENTES (PCT)

(19) Organización Mundial de Propiedad  
Intelectual  
Oficina Internacional



(43) Fecha de Publicación Internacional  
12 de Junio de 2008 (12.06.2008)

PCT

(10) Número de Publicación Internacional  
WO 2008/068770 A3

- (51) Clasificación Internacional de Patentes:  
A61K 31/277 (2006.01) A61K 31/167 (2006.01)  
A61K 31/10 (2006.01)
- (21) Número de Solicitud Internacional:  
PCT/IN2007/000274
- (22) Fecha de Presentación Internacional:  
05 de Julio de 2007 (05.07.2007)
- (25) Lenguaje de entrega: Inglés
- (26) Lenguaje de Publicación: Inglés
- (30) Datos de la Prioridad:  
1074/MUM/2006 07 de Julio de 2006 (07.07.2006) IN
- (71) Solicitante (para todos los Estados designados menos los Estados Unidos): **PANACEA BIOTEC LTD.** [IN/IN]; B-1 Extn./A-27, Mohan Co-operative Industrial Estate, Mathura Road, New Delhi 110 044 (IN).
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- (81) Estados Designados (a menos que se indique lo contrario, para todo tipo de protección nacional disponible): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
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**Declaraciones bajo la Regla 4.17:**

- según los derechos del solicitante para solicitar y otorgársele una patente (Regla 4.17(ii))
- según los derechos del solicitante para reclamar la prioridad de la solicitud anterior (Regla 4.17(iii))
- del inventor (Regla 4.17(iv))

**Publicado:**

- con el Informe de búsqueda internacional
- antes de la fecha límite de expiración para reivindicaciones modificadas y a ser republicado nuevamente en el evento de recibirlas

- (88) Fecha de publicación del Reporte de Búsqueda Internacional

16 de Octubre de 2008

(54) Título: COMPOSICIÓN FARMACÉUTICA QUE CONTIENE BICALUTAMIDA Y UN MÉTODO PARA SU USO

(57) Resumen: La invención se refiere a una formulación oral que contiene bicalutamida con un patrón de liberación modificada; la composición es adecuada para ser administrada en un programa de dosificación de tres veces a la semana, dos veces a la semana y una vez a la semana; la composición se usa para producir un efecto antiandrogénico.

**COMPOSICION FARMACEUTICA QUE CONTIENE BICALUTAMIDA Y UN****METODO PARA SU USO****CAMPO DE LA INVENCION**

5

Esta invención pertenece al campo de las ciencias farmacéuticas. Se refiere a métodos y composiciones de bicalutamida, un compuesto antiandrogénico no esteroideo.

10

**ANTECEDENTES DE LA INVENCION**

Los andrógenos son compuestos naturales o sintéticos, usualmente hormonas esteroides, que estimulan y controlan el desarrollo y mantenimiento de las características masculinas mediante su unión a los receptores de andrógeno. Al ser esteroides anabólicos, se sabe que estimulan el crecimiento de algunos tejidos como los de la próstata y otros tejidos periféricos, incluyendo células de tumor de próstata primario o metastásico. Los andrógenos como la testosterona y la dihidrotestosterona ejercen su influencia sobre las funciones celulares uniéndose a los receptores de andrógeno. La alta proporción de respuesta a la "terapia de privación de andrógeno" de primera línea, y la presencia de receptores de andrógeno en las células de tumor de próstata tanto primario como metastásico, apoyan la idea de que el receptor es un mediador importante del desarrollo y crecimiento

del cáncer de próstata.

Los carcinomas prostáticos son dependientes de andrógeno; por lo tanto, varias estrategias de tratamiento se enfocan en abolir la función de los andrógenos (esto es, la testosterona y la dihidrotestosterona) en el crecimiento del tumor de próstata. Estas estrategias de tratamiento incluyen el uso de análogos de la hormona liberadora de hormona luteinizante ("LHRH") para suprimir la producción testicular de andrógeno (castración química) u orquiectomía (castración quirúrgica) para eliminar la producción de andrógeno.

En años recientes una clase de fármacos conocida como antiandrógenos se ha usado para el tratamiento del cáncer de próstata. La actividad biológica de los andrógenos es mediada por la formación de un complejo no covalente de receptor de andrógeno-esteroide. Los antiandrógenos inhiben la formación de este complejo y por lo tanto suprimen la función de los esteroides endógenos en el crecimiento de la próstata dependiente de andrógeno.

También se han estudiado en varios casos combinaciones de las estrategias anteriormente mencionadas para evaluar las eficacias relativas y los beneficios de supervivencia. Una combinación de fármacos antiandrogénicos con castración (química o quirúrgica), no solo impide la acción de la testosterona producida por los testículos, sino que también la cantidad pequeña pero importante que es producida por otras glándulas, esto es, las glándulas adrenales. Dicha terapia algunas veces es denominada

Bloqueo de Andrógeno Completo o Máximo (CAB o MAB). En la enfermedad avanzada se puede usar una combinación de un análogo de LHRH (por ejemplo, goserelina, leuprolida) (administrado generalmente como implantes o depósitos inyectables de acción prolongada), y un antiandrógeno no esteroideo (por ejemplo, bicalutamida administrada como tabletas orales). Las pruebas clínicas identifican que los hombres tratados con dicha terapia de combinación pueden vivir más tiempo que los tratados con un análogo de LHRH solo. Algunas veces la terapia de combinación también se puede usar antes de la cirugía o la radioterapia (neoadyuvante) para reducir el tamaño del tumor.

La bicalutamida, una acilanilida, es un antiandrógeno no esteroideo; es un antiandrógeno de "segunda generación" que tiene propiedades más ventajosas que los otros antiandrógenos conocidos, como flutamida o nilutamida (véase por ejemplo Schellhammer PF y otros, *Urology*, 50: 330-6 (1997); y Mcleod DG, *Oncologist*, 2:18-27 (1997)). El producto disponible comercialmente de AstraZeneca es CASODEX<sup>(TM)</sup> y su nombre químico es 4-ciano-3-trifluorometil-N-(3-p-fluorofenilsulfonil-2-hidroxi-2-metilpropionil)anilina. El compuesto se ha descrito en patentes como la patente de EE. UU. No. 4636505 y la patente Europea No. 100172. Su actividad antiandrogénica reside casi exclusivamente en la (R)-bicalutamida, con poca o ninguna actividad de (S)-bicalutamida. Se usa a una dosis de 50 mg una vez al día, en combinación con un análogo de la hormona liberadora de hormona luteinizante o castración quirúrgica para el tratamiento del cáncer

de próstata avanzado. También se administra a una dosis de 150 mg una vez al día como monoterapia para el tratamiento del cáncer de próstata temprano (localizado o avanzado localmente) sin metástasis. Tiene una vida media prolongada de aproximadamente 5.8 días, y el tiempo para alcanzar la  
5 concentración plasmática pico es de aproximadamente 31 horas.

Reportes detallados de la bicalutamida informan que después de la administración diaria de bicalutamida a los pacientes, la relación entre la concentración de estado estable (C<sub>ss</sub>) y la dosis es lineal solo entre 10 mg/día y 50 mg/día, se desvía de la linealidad a dosis entre 100 mg y 200 mg por día,  
10 y se desvía más de la linealidad a 300 mg/día. Por arriba de 300 mg, especialmente cuando se estudia a una dosis de 450 mg y 600 mg, no se observa mayor incremento en la C<sub>ss</sub>. Esta falta de linealidad y meseta en la C<sub>ss</sub> a dosis más altas se han atribuido a una disminución de la absorción del fármaco y transporte saturable a través del tracto GI; véase Tyrell CJ y otros,  
15 *Eur Urol* 33:39-53 (1998).

El cáncer de próstata más frecuentemente avanza muy lentamente y a menudo muchos pacientes no tienen síntomas, particularmente en las etapas tempranas. La mayoría de los hombres con cáncer de próstata viven con su enfermedad durante muchos años. Por lo  
20 tanto es importante considerar su elección cuando se enfrentan a las terapias de privación de andrógeno anteriormente mencionadas. Por ejemplo, véase Nyman y otros, *BJU International*, 96: 1014 – 1018 (2005), en donde se realizó un estudio Sueco en 150 pacientes para investigar su elección entre las tres

terapias de privación de andrógeno: bicalutamida, análogo de GnRH y orquiectomía. La mayoría de los hombres prefirieron tabletas orales del antiandrógeno bicalutamida, pero también indicaron insatisfacción; una de las principales razones fue la necesidad de tomar el fármaco todos los días. La bicalutamida se usa frecuentemente durante meses hasta años juntos. Por lo tanto, en dichas situaciones, se hace difícil tomar los medicamentos diariamente y existe la necesidad de una terapia que reduzca la frecuencia de dosificación, aumentando así la comodidad y cumplimiento del paciente.

La solicitud de EE. UU. No. 2004067257 describe dispersiones sólidas de bicalutamida con polímeros entéricos que tienen un pKa de 3 a 6 para aumentar la biodisponibilidad del fármaco, para reducir la variabilidad entre pacientes en las concentraciones plasmáticas de bicalutamida, o para tratar o reducir el riesgo del cáncer de próstata en un paciente. El paciente tiene que tomar la dosis farmacéutica diariamente.

La publicación internacional WO2006069098 describe formulaciones de bicalutamida en nanopartículas, que tienen partículas de bicalutamida con un tamaño de partícula promedio efectivo menor de aproximadamente 2000 nm, y que contienen estabilizadores de superficie, que alcanzan un aumento de la biodisponibilidad del fármaco. La publicación enseña composiciones que se pueden formular para inyección parenteral (por ejemplo, intravenosa, intramuscular o subcutánea), administración oral en forma sólida, líquida o aerosol, o administración vaginal, nasal, rectal, ocular, local (polvos, ungüentos o gotas), bucal, intracisternal, intraperitoneal, o

tópica, etc. La invención se refiere a aumentar la solubilidad y biodisponibilidad de la bicalutamida.

La publicación internacional WO2006076533 describe composiciones de liberación controlada de partículas de acilanolida, particularmente bicalutamida, para usarse en terapia de combinación y que tienen la finalidad de suministrar el ingrediente activo de una manera impulsada o bimodal por administración oral. Las composiciones son de multipartículas, en donde los impulsos subsiguientes se obtienen recubriendo la población de partículas. No se dan detalles de la formulación ni tampoco ejemplos. Las composiciones están destinadas para administración una vez al día.

La publicación internacional WO2006090129 se refiere a un método de tratamiento del cáncer de próstata metastásico administrando formulaciones de bicalutamida que suministran concentraciones plasmáticas medias de estado estable de R-bicalutamida de por lo menos 40 ug/ml. Los ejemplos dados en la solicitud se relacionan principalmente con dispersiones sólidas y formulaciones de R-bicalutamida, destinadas para su administración diaria.

Anteriormente se ha intentado mejorar la absorción y biodisponibilidad de la bicalutamida a dosis más altas, pero todavía existe la necesidad de desarrollar y proveer una composición de bicalutamida que pueda superar la absorción saturable y proveer una relación lineal entre la concentración de estado estable y la dosis en una amplia escala de dosis, de

aproximadamente 50 mg a aproximadamente 600 mg.

También es deseable tener un método para producir un efecto antiandrogénico en un mamífero, suministrando bicalutamida con una menor frecuencia de dosis y manteniendo sus concentraciones terapéuticamente efectivas durante un periodo prolongado. Para dicho método, aunque la dosis administrada durante un intervalo de dosificación puede ser igual o menor a la dosis total administrada durante el intervalo con la terapia convencional de una vez al día, el método utiliza una dosis de una sola vez más alta que una dosis convencional de una vez al día. Esta dosis puede ser de 150 mg o más alta, esto es, más alta que la dosis unitaria de una vez al día. Sin embargo, como se sabe, para altas dosis, la bicalutamida exhibe una cinética no lineal debido posiblemente a su absorción saturable (véase también Kolvenbag y otros, *Prostate*, 34:61-72 (1998)). Por lo tanto, la inclusión de dichas dosis puede resultar en absorción incompleta, llevando a concentraciones de fármaco subóptimas en el plasma. Además, a dosis más altas, se ha informado de una variabilidad alta de la farmacocinética de la bicalutamida entre los pacientes.

Por lo tanto, existe la necesidad de un método para producir un efecto antiandrógeno en un mamífero en necesidad del mismo que solucione los anteriores problemas y otros más.

### **BREVE DESCRIPCION DE LA INVENCION**

Los inventores han encontrado ahora que, contrario a la saturación esperada de la absorción de bicalutamida, es posible administrar  
5 bicalutamida a dosis más altas, de modo que las concentraciones plasmáticas terapéuticamente efectivas del fármaco se mantienen en la sangre durante un periodo prolongado.

El método y la composición de la presente invención proveen el mantenimiento de la concentración plasmática terapéuticamente efectiva de la  
10 bicalutamida durante un periodo prolongado, y por lo tanto permiten reducir la frecuencia de dosificación.

Un aspecto de la presente invención se refiere a un método para producir un efecto antiandrogénico en un mamífero en necesidad del mismo, mediante la administración oral de una cantidad farmacéuticamente efectiva  
15 de bicalutamida con una menor frecuencia de dosificación, por ejemplo una dosificación de tres veces a la semana, dos veces a la semana y una vez a la semana.

Otro aspecto de la presente invención se refiere a un método de producción de un efecto antiandrogénico en un mamífero, administrando por  
20 vía oral al mamífero una composición farmacéutica de bicalutamida de liberación modificada en un programa de dosificación de una vez a la semana.

La presente invención provee una composición de administración una vez a la semana que contiene bicalutamida para producir un efecto

antiandrogénico en un mamífero.

Un aspecto de la presente invención también se refiere a una cantidad farmacéuticamente efectiva de bicalutamida que varía de aproximadamente 50 mg a aproximadamente 1000 mg, y que es efectiva para el método de la invención.

Otro aspecto en la presente invención se refiere a una composición farmacéutica de bicalutamida de liberación modificada que exhibe una mayor biodisponibilidad y un perfil farmacocinético mejorado de la bicalutamida. La composición es una composición de liberación impulsada oral en donde una parte de la dosis de bicalutamida se libera de manera sustancialmente inmediata tras su administración, y la parte restante de la dosis se libera después de un intervalo predeterminado. La porción de liberación inmediata se formula en forma de por lo menos una tableta recubierta con película o no recubierta, y una porción de liberación retardada se formula en forma de por lo menos una tableta recubierta con polímeros de liberación retardada.

#### **BREVE DESCRIPCION DE LOS DIBUJOS**

La figura 1 muestra los perfiles de tiempo de la concentración plasmática predicha de composiciones de bicalutamida de prueba y de referencia en valores de estado estable, en comparación con la referencia predicha de 50 mg de bicalutamida administrados diariamente.

La figura 2 muestra el perfil de disolución de una composición ilustrativa de bicalutamida ("prueba") del ejemplo 3.

### **DESCRIPCION DETALLADA DE LA INVENCION**

5

La presente invención se refiere a un método, preferiblemente un método oral, para producir un efecto antiandrogénico en un mamífero en necesidad del mismo.

El método es provisto por la administración oral a un mamífero  
10 de una composición farmacéutica de bicalutamida de liberación modificada, que se administra en un programa de dosificación de tres veces a la semana, dos veces a la semana, o una vez a la semana.

Preferiblemente, la composición farmacéutica de bicalutamida de liberación modificada se administra en un programa de dosificación de una  
15 vez a la semana.

El método de la invención provee un mantenimiento prolongado de concentraciones plasmáticas terapéuticamente efectivas de bicalutamida en el cuerpo. La frecuencia de dosificación se reduce suministrando una composición farmacéutica de liberación modificada que reduce las pérdidas  
20 de bicalutamida debido a la saturación de los mecanismos de absorción. Además, el método de la presente invención mejora el cumplimiento del paciente puesto que se evita la inconveniencia de la dosificación diaria. El método también puede reducir la variabilidad entre pacientes.

El término "bicalutamida", como se usa aquí, contempla todas las formas de bicalutamida, tales como la base libre, cualquier sal farmacéuticamente aceptable, ésteres, y solvatos de la misma, así como también el racemato, los isómeros individuales R-bicalutamida y S-bicalutamida y sus sales farmacéuticamente aceptables, ésteres y solvatos. Por consiguiente, la bicalutamida se usa en la composición farmacéutica de la presente invención en una escala de cantidades equivalentes de aproximadamente 50 mg a aproximadamente 1000 mg de bicalutamida.

"Programa de dosificación de tres veces a la semana", como se usa aquí, significa que una dosis de bicalutamida se administra tres veces a la semana, es decir, tres veces durante un periodo de siete días, preferiblemente los mismos tres días de cada periodo semanal.

Un programa de dosificación de "dos veces a la semana", como se usa aquí, significa que una dosis de bicalutamida se administra dos veces a la semana, es decir, dos veces durante un periodo de siete días, preferiblemente los mismos dos días de cada periodo semanal.

El término programa de dosificación de "una vez a la semana", como se usa aquí, significa que una dosis de bicalutamida se administra una vez a la semana, es decir, una vez durante un periodo de siete días, preferiblemente el mismo día de cada semana.

El término "cantidad farmacéuticamente efectiva" de bicalutamida, como se usa aquí, indica una cantidad de bicalutamida que se requiere administrar a un mamífero para obtener un resultado terapéutico

deseado, especialmente un efecto antiandrogénico. La dosis utilizada para el propósito anterior será por lo general de aproximadamente 50 mg a aproximadamente 1000 mg.

“Frecuencia de dosificación reducida”, como se usa aquí, significa que la frecuencia de administración de bicalutamida a un mamífero es menor a una vez al día. De esta manera, por ejemplo, la frecuencia puede ser tres veces a la semana, dos veces a la semana o una vez a la semana.

En general, el método de la presente invención es aplicable a un mamífero en necesidad de terapia antiandrogénica. Preferiblemente, el mamífero es un paciente humano, preferiblemente masculino, y particularmente un varón que ha sido identificado por padecer trastornos proliferativos, tales como cáncer de próstata, hiperplasia prostática benigna o posiblemente cualquier otro cáncer genitourinario.

Un aspecto del método de la presente invención contempla administrar la composición de bicalutamida de la presente invención sola y también en combinación con otros agentes farmacéuticos tales como antiestrógenos, por ejemplo tamoxifeno; inhibidores de aromatasa, por ejemplo anastrozol; análogos de LH-RH, por ejemplo goserelina; agentes citotóxicos como ciclofosfamida; y cualquier otro agente adecuado. La composición también se puede administrar como un auxiliar con orquiectomía.

Otro aspecto del método de la presente invención contempla la administración de una o más dosis de carga de bicalutamida, seguida por la administración de la composición de la invención como una terapia de

mantenimiento. Esto permitirá obtener rápidamente concentraciones de estado estable, seguido por su mantenimiento durante el periodo de la terapia.

La composición de la invención se administra como una dosis unitaria y la dosis unitaria puede variar de aproximadamente 50 mg a aproximadamente 1000 mg de bicalutamida. Preferiblemente varía de aproximadamente 150 mg a aproximadamente 600 mg, de preferencia de aproximadamente 150 mg a aproximadamente 400 mg de bicalutamida, administrada en un programa de dosificación de tres veces a la semana, dos veces a la semana, o una vez a la semana.

La composición farmacéutica de liberación modificada de la presente invención comprende bicalutamida y excipientes adecuados. La composición puede mostrar cualquier tipo de perfil de liberación modificada que permita reducir la frecuencia de dosificación. De esta manera, el perfil de liberación modificada de acuerdo con la invención puede ser una liberación controlada, liberación sostenida, liberación prolongada, liberación retardada, liberación impulsada, liberación doble, liberación cronometrada, liberación específica de sitio y otras, incluyendo cualquier combinación de las mismas.

En una modalidad de la invención, la composición está en forma de un producto oral de liberación retardada, en donde tras su administración la dosis completa de bicalutamida es liberada después de un intervalo predeterminado en la parte final del tracto gastrointestinal. La liberación puede ser "todo a la vez" o de una manera sostenida.

En una modalidad de la invención, la composición está en forma

de un producto oral de liberación impulsada, en donde una parte de la dosis de bicalutamida es liberada de forma sustancialmente inmediata tras su administración, y la parte restante de la dosis es liberada después de un intervalo de tiempo predeterminado.

- 5                    La composición de las modalidades anteriores puede incluir varios excipientes farmacéuticamente aceptables, por ejemplo diluentes como celulosa microcristalina, lactosa, sacarosa, fosfatos de calcio; desintegrantes como almidón, derivados de celulosa, gomas, polímeros entrelazados y similares; aglutinantes como almidón, gelatina, azúcares, derivados de
- 10                    celulosa, polivinilpirrolidona, etc.; lubricantes como talco, estearato de magnesio, dióxido de silicio coloidal, polietilenglicol, y mezclas de los mismos.

- La composición se puede formular en forma de gránulos, tabletas, tabletas estratificadas, minitabledas y pellas, o como cápsulas llenas con polvo, pellas, minitabledas o tabletas. El procedimiento de preparación de
- 15                    estas composiciones es muy conocido y se incluye en la presente como referencia.

- En una modalidad, la bicalutamida y excipientes adecuados se formulan juntos en forma de gránulos. Los gránulos se comprimen para formar minitabledas de bicalutamida. Opcionalmente se recubren con una
- 20                    película. Estas minitabledas liberan la bicalutamida de forma sustancialmente inmediata tras la administración de la composición. Después, las minitabledas se recubren con polímeros adecuados que modifican la velocidad y tiempo de liberación de la bicalutamida. Generalmente estos polímeros pertenecen a

categorías tales como celulosas, polímeros de vinilpirrolidona, homopolímeros de óxido de alquileo, polímeros superdesintegrantes, polímeros de ácido acrílico y gomas de origen vegetal, animal, mineral o sintético.

Preferiblemente, los polímeros retrasan la liberación de la bicalutamida hasta un intervalo de tiempo predeterminado. Para este fin se prefieren polímeros entéricos, tales como los ésteres de celulosa y sus derivados, polímeros y copolímeros de vinilo, copolímeros de ácido metacrílico sensibles al pH, goma laca, etc. Algunos ejemplos que se pueden usar en las composiciones de la invención son acetatoftalato de celulosa, acetatosuccinato de celulosa, ftalato de metilcelulosa, ftalato de etilhidroxixelulosa, acetatoftalato de polivinilo, acetatobutirato de polivinilo, copolímero de acetato de vinilo-anhídrido maleico, copolímero de estireno-monoéster maleico, copolímero de acrilato de metilo-ácido metacrílico, copolímero de metacrilato-ácido metacrílico-acrilato de octilo, etc.

En una modalidad, una cápsula dura de gelatina se llena con las minitabletas recubiertas, que corresponden a la dosis total de bicalutamida por administrar, para formar la composición de liberación retardada de la invención.

En una modalidad preferida, una cápsula dura de gelatina se llena con una combinación de minitabletas no recubiertas (o recubiertas con película) y minitabletas recubiertas. El número de minitabletas recubiertas y no recubiertas con que se llena la cápsula depende de la cantidad de bicalutamida por liberar inmediatamente y después de un periodo

predeterminado del tiempo de administración. En las minitabletas no recubiertas para liberación inmediata se incluyen de aproximadamente 80 mg a aproximadamente 600 mg de bicalutamida, y en las minitabletas recubiertas para liberación retardada se incluyen de aproximadamente 60 mg a 5 aproximadamente 400 mg de bicalutamida.

En una modalidad alternativa, la composición se formula en forma de una sola tableta que consiste en un núcleo que contiene bicalutamida, recubierta con uno o más polímeros que modifican la velocidad de liberación del fármaco.

10 En otra modalidad alternativa, la composición se puede formular como una composición de matriz, en donde la bicalutamida y el polímero adecuado se mezclan entre sí para formar una matriz que modifica la liberación de la bicalutamida.

En otras modalidades, la composición se da como parte de un 15 equipo de comprende agentes de terapia de combinación. Otros agentes que se pueden incluir como parte del equipo son antiestrógenos, por ejemplo tamoxifeno; inhibidores de aromatasa, por ejemplo anastrozol; análogos de LH-RH, por ejemplo goserelina; agentes citotóxicos como ciclofosfamida; y cualquier otro agente adecuado. En otro aspecto, la composición del equipo 20 se administra diariamente, hasta un máximo de cuatro semanas, o hasta alcanzar un estado estable, como una dosis de carga, seguido por la administración semanal de la misma composición como una dosis de mantenimiento.

El segundo aspecto de la invención se refiere a una composición farmacéutica de bicalutamida de liberación modificada. Se ha encontrado sorprendentemente que cuando la composición se formula como una combinación de componentes de liberación inmediata y liberación retardada de una manera específica, hay un aumento sustancial de las concentraciones plasmáticas de bicalutamida. También se ha encontrado sorprendentemente que el área bajo la curva y las concentraciones plasmáticas de bicalutamida, administrada usando la composición anterior, son más altas en comparación con una dosis similar administrada en una composición de bicalutamida convencional.

La composición es una composición oral sólida, en donde el componente de liberación inmediata se formula como una tableta no recubierta o una tableta recubierta con película que se dispersa para liberar la bicalutamida de forma sustancialmente inmediata después de su administración oral. El componente de liberación retardada se formula recubriendo la tableta no recubierta con polímeros que retardan la liberación de la bicalutamida durante un intervalo de tiempo predeterminado. Preferiblemente, los polímeros son polímeros entéricos seleccionados del grupo de ésteres de celulosa y sus derivados, polímeros y copolímeros de vinilo, y copolímeros de ácido metacrílico sensibles al pH. Las tabletas no recubiertas o recubiertas con película, y las tabletas recubiertas de liberación retardada, se combinan para formar la composición de liberación modificada de la invención.

Esta composición se puede usar para obtener mayor eficacia y mejor tratamiento del cáncer de próstata avanzado, avanzado localmente no metastático, y también metastático. La dosis del régimen de dosificación se puede seleccionar adecuadamente dependiendo de las necesidades y estado  
5 de enfermedad de los pacientes, y dependiendo de si se administra como parte de una terapia de combinación o como una monoterapia.

Una modalidad de esta composición que muestra mayor biodisponibilidad en comparación con una composición convencional de bicalutamida, es una composición farmacéutica de bicalutamida de liberación  
10 modificada que es una composición de liberación impulsada oral formulada como una combinación de componentes de liberación inmediata y liberación retardada, que comprende bicalutamida en una cantidad de aproximadamente 20% a aproximadamente 80% de la dosis total en el componente de liberación inmediata, y en una cantidad de aproximadamente 80% a aproximadamente  
15 20% de la dosis total en el componente de liberación retardada.

En una modalidad específica, cuando la composición farmacéutica de liberación modificada se somete a pruebas de disolución usando un aparato USP de tipo I, usando el método de cambio del pH con fluido gástrico simulado de pH 1.2, amortiguador de pH 4.5 y fluido intestinal  
20 simulado de pH 6.8, libera la bicalutamida de acuerdo con el siguiente perfil de disolución: se libera entre 20% y 65% de bicalutamida en el fluido gástrico simulado; se libera entre 40% y 75% en el amortiguador de pH 4.5; y se libera no menos de 60% en fluido intestinal simulado. El medio de disolución

comprende 1% de laurilsulfato de sodio y la composición se puede probar en fluido gástrico simulado durante 2 horas aproximadamente, en un amortiguador de pH 4.5 durante 2 horas aproximadamente, y en el fluido intestinal simulado durante el periodo restante.

5

#### Estudio clínico

Se diseñó un estudio en un grupo pequeño de voluntarios para evaluar la farmacocinética de la administración de una sola dosis de la composición de la invención, y se comparó con la farmacocinética de una dosis similar de Casodex® durante un periodo de una semana.

Diseño del estudio: Estudio farmacocinético aleatorizado abierto de una sola dosis en ayunas, usando un diseño de estudio en paralelo. Se usaron 12 voluntarios humanos sanos (6 voluntarios para cada grupo). La composición de prueba comprendió 250 mg de bicalutamida y se formuló para liberar parte de la dosis inmediatamente después de la administración, y parte de la dosis después de un intervalo de tiempo predeterminado. La composición de referencia fue cinco tabletas de 50 mg de Casodex® administradas juntas. La muestra de sangre se realizó antes de la dosis y después de intervalos de tiempo predeterminados por más de una semana. Los parámetros farmacocinéticos valorados fueron C<sub>max</sub>, T<sub>max</sub>, AUC<sub>t</sub> y AUC<sub>inf</sub>.

#### Resultados

Los datos farmacocinéticas derivados de la prueba se dan en el cuadro 1 siguiente:

**CUADRO 1**

5

| Producto | N<br>Obs | Parámetro        | N | Media     |
|----------|----------|------------------|---|-----------|
| R        | 6        | Cmax (ng/ml)     | 6 | 1774.43   |
|          |          | ABCt (ng.h/ml)   | 6 | 201978.96 |
|          |          | ABCinf (ng.h/ml) | 6 | 325810.62 |
| T        | 6        | Cmax (ng/ml)     | 6 | 1928.17   |
|          |          | ABCt (ng.h/ml)   | 6 | 231661.88 |
|          |          | ABCinf (ng.h/ml) | 6 | 489684.23 |

10                    Como se observa en el cuadro, el ABCinf para el producto de prueba es aproximadamente 1.5 veces mayor que el ABCinf para el producto de referencia, indicando un incremento de absorción y biodisponibilidad obtenido con la composición de la presente invención. El incremento de absorción será útil en la acumulación más rápida de concentraciones de

15 estado estable, además de reducir la dosis/frecuencia de dosificación.

Para predecir y comparar la cinética de las composiciones de prueba y referencia en estado estable, los datos de la prueba se cargaron en el software Winnonlin®. En la figura 1 se muestran los perfiles de tiempo de concentración plasmática predichos de las composiciones de prueba y de

20 referencia a concentraciones de estado estable.

Como puede verse en la figura, el método y la composición de la invención darán como resultado un perfil plasmático mejorado de la bicalutamida en comparación con el producto de referencia. También, la

concentración plasmática mantenida con la administración una vez a la semana durante una semana, puede ser comparable o más alta que la concentración plasmática predicha de la administración diaria de 50 mg de la referencia.

5                      Los parámetros farmacocinéticos de estado estable se predijeron para los productos de prueba y referencia el día 85 después de la dosificación. Los datos se presentan en el cuadro 2 siguiente.

**CUADRO 2**

10

| Parámetro            | Medias de mínimos cuadrados |            | Relación | 90% de Intervalo de confianza |          |
|----------------------|-----------------------------|------------|----------|-------------------------------|----------|
|                      | Prueba                      | Referencia |          | Inferior                      | Superior |
| ABC 0-τ<br>(ng-h/mL) | 437704                      | 320207     | 1.367    | 0.921                         | 1.813    |
| Cmax<br>(ng/mL)      | 3417                        | 2625       | 1.302    | 0.972                         | 1.631    |
| Cmin<br>(ng/mL)      | 1805                        | 1148       | 1.572    | 0.907                         | 2.236    |
| 15 Tmax<br>(horas)   | 32.8                        | 27.7       | 1.184    | -                             | -        |
| T½<br>(horas)        | 131                         | 105        | 1.251    | -                             | -        |
| Fluctuación<br>(%)   | 67.9                        | 81.1       | 0.836    | -                             | -        |

20                      Como puede verse en el cuadro 2 anterior, para todos los parámetros farmacocinéticas de estado estable predichos, el producto de prueba tuvo un valor más alto que el producto de referencia, y el producto de prueba tuvo menos fluctuación en comparación con el producto de referencia,

indicando una mejor absorción y biodisponibilidad y una vida media prolongada del producto de prueba, así como también un potencial de variabilidad reducida. Se pueden hacer varias modificaciones del método de la invención sin apartarse del espíritu o alcance de la invención. Los siguientes ejemplos no limitativos ilustran una modalidad de la invención y no se debe considerar que limitan el alcance de la invención.

**EJEMPLO 1**

10

**CUADRO 3**

**Fórmula de núcleo de tableta**

15

| No. serie | Ingrediente                | Cantidad (mg/tab) |
|-----------|----------------------------|-------------------|
| 1         | Bicalutamida               | 250.00            |
| 2         | Lactosa monohidratada      | 188.00            |
| 3         | Almidón glicolato de sodio | 35.00             |
| 4         | Polivinilpirrolidona       | 7.50              |
| 5         | Agua purificada            | c.s.              |
| 6         | Almidón glicolato de sodio | 17.50             |
| 7         | Estearato de magnesio      | 2.00              |

**CUADRO 4**

20

**Fórmula de composición de sub-recubrimiento**

| No. serie | Ingrediente                 | Cantidad (g/kg) |
|-----------|-----------------------------|-----------------|
| 1         | Hidroxipropilmetilcelulosa  | 50.00           |
| 2         | Polietilenglicol (PEG 6000) | 7.50            |
| 3         | Metanol                     | 628.30          |
| 4         | Diclorometano               | 314.20          |

**CUADRO 5**

**Fórmula de la composición de recubrimiento entérico**

5

| No. serie | Ingrediente                                                                                     | Cantidad (g/kg) |
|-----------|-------------------------------------------------------------------------------------------------|-----------------|
| 1         | Copolímero de ácido metacrílico (copolímero de ácido metacrílico – metacrilato de metilo (1:2)) | 53.85           |
| 2         | Copolímero de ácido metacrílico (copolímero de ácido metacrílico – metacrilato de metilo (1:1)) | 23.07           |
| 3         | Citrato de trietilo                                                                             | 15.38           |
| 4         | Acetona                                                                                         | 276.92          |
| 5         | Alcohol isopropílico                                                                            | 553.07          |
| 6         | Agua purificada                                                                                 | 39.23           |
| 7         | Talco                                                                                           | 38.46           |

10

La bicalutamida, el almidón glicolato de sodio (porción intragranular) y la lactosa monohidratada se tamizaron y se mezclaron en las cantidades indicadas arriba en el cuadro 2. Se usó polivinilpirrolidona disuelta en una cantidad suficiente de agua purificada para granular la mezcla de polvos secos.

La mezcla se secó y se tamizó para obtener gránulos secos. Después, los gránulos se mezclaron con la cantidad restante de almidón glicolato de sodio y estearato de magnesio. La mezcla lubricada se comprimió en tabletas usando punzones redondos.

La solución de sub-recubrimiento se preparó disolviendo PEG 6000 e hidroxipropilmetilcelulosa en la mezcla de metanol y diclorometano.

Las tabletas se recubrieron usando esta solución hasta obtener una ganancia en peso de tableta de 2-3% aproximadamente.

La dispersión de recubrimiento entérico se preparó mezclando acetona, isopropanol y agua purificada y dispersando en ellos los copolímeros de ácido metacrílico, talco y citrato de trietilo. Las tabletas sub-recubiertas se recubrieron con la solución anterior hasta obtener una ganancia en peso de 10-11%.

**EJEMPLO 2**

10

**CUADRO 6**

**Fórmula de núcleo de tableta**

15

| No. serie | Ingrediente                | Cantidad (mg/tab) |
|-----------|----------------------------|-------------------|
| 1         | Bicalutamida               | 50.00             |
| 2         | Lactosa monohidratada      | 37.60             |
| 3         | Almidón glicolato de sodio | 7.00              |
| 4         | Polivinilpirrolidona       | 1.50              |
| 5         | Agua purificada            | c.s.              |
| 6         | Almidón glicolato de sodio | 3.50              |
| 7         | Estearato de magnesio      | 0.40              |

**CUADRO 7**

**Fórmula de composición de sub-recubrimiento**

5

| No. serie | Ingrediente                 | Cantidad (g/kg) |
|-----------|-----------------------------|-----------------|
| 1         | Hidroxipropilmetilcelulosa  | 50.00           |
| 2         | Polietilenglicol (PEG 6000) | 7.50            |
| 3         | Metanol                     | 628.30          |
| 4         | Diclorometano               | 314.20          |

**CUADRO 8**

**Fórmula de la composición de recubrimiento entérico**

10

| No. serie | Ingrediente                                                                                     | Cantidad (g/kg) |
|-----------|-------------------------------------------------------------------------------------------------|-----------------|
| 1         | Copolímero de ácido metacrílico (copolímero de ácido metacrílico – metacrilato de metilo (1:2)) | 53.85           |
| 2         | Copolímero de ácido metacrílico (copolímero de ácido metacrílico – metacrilato de metilo (1:1)) | 23.07           |
| 3         | Citrato de trietilo                                                                             | 15.38           |
| 4         | Acetona                                                                                         | 276.92          |
| 5         | Alcohol isopropílico                                                                            | 553.07          |
| 6         | Agua purificada                                                                                 | 39.23           |
| 7         | Talco                                                                                           | 38.46           |

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El procedimiento fue el mismo del ejemplo 1. Las tabletas que corresponden a una dosis total de 250 mg de bicalutamida (esto es, cinco tabletas recubiertas), se introdujeron en una cápsula dura de gelatina.

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EJEMPLO 3

CUADRO 9

Fórmula de núcleo de tableta

| No. serie | Ingrediente                | Cantidad (mg/tab) |
|-----------|----------------------------|-------------------|
| 1         | Bicalutamida (micronizada) | 50.00             |
| 2         | Lactosa monohidratada      | 61.00             |
| 3         | Almidón glicolato de sodio | 11.20             |
| 4         | Polivinilpirrolidona       | 2.40              |
| 5         | Agua purificada            | c.s.              |
| 6         | Almidón glicolato de sodio | 4.60              |
| 7         | Estearato de magnesio      | 0.60              |

CUADRO 10

Fórmula de composición de sub-recubrimiento

| No. serie | Ingrediente                                    | Cantidad (g/kg) |
|-----------|------------------------------------------------|-----------------|
| 1         | Opadry (polvo de recubrimiento de hipromelosa) | 100             |
| 2         | Agua purificada                                | 900             |

**CUADRO 11**

**Fórmula de la composición de recubrimiento entérico**

| No. serie | Ingrediente                                                                                     | Cantidad (g/kg) |
|-----------|-------------------------------------------------------------------------------------------------|-----------------|
| 1         | Copolímero de ácido metacrílico (copolímero de ácido metacrílico – metacrilato de metilo (1:2)) | 53.850          |
| 2         | Copolímero de ácido metacrílico (copolímero de ácido metacrílico – metacrilato de metilo (1:1)) | 23.078          |
| 3         | Citrato de trietilo                                                                             | 15.386          |
| 4         | Acetona                                                                                         | 276.920         |
| 5         | Alcohol isopropílico                                                                            | 553.077         |
| 6         | Agua purificada                                                                                 | 39.230          |
| 7         | Talco                                                                                           | 38.460          |

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El procedimiento fue el mismo del ejemplo 1. Las tabletas no recubiertas que corresponden a una dosis total de 150 mg, y dos tabletas sin recubrir que corresponden a una dosis total de 100 mg, se introdujeron en una cápsula dura de gelatina. La composición se sometió a un estudio de disolución usando el método del cambio del pH, usando amortiguadores de pH 1.2, 4.5 y 6.8 con laurilsulfato de sodio (SLS) al 1%. El estudio se efectuó en un aparato USP de tipo I. El perfil de disolución obtenido se indica en la figura 2.

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**EJEMPLO 4**

**CUADRO 12**

**Fórmula de núcleo de tableta**

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| No. serie | Ingrediente                | Cantidad (mg/tab) |
|-----------|----------------------------|-------------------|
| 1         | Bicalutamida               | 350.00            |
| 2         | Lactosa monohidratada      | 199.60            |
| 3         | Polivinilpirrolidona       | 18.00             |
| 4         | Almidón glicolato de sodio | 30.00             |
| 5         | Estearato de magnesio      | 2.40              |

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**CUADRO 13**

**Fórmula de composición de sub-recubrimiento**

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| No. serie | Ingrediente                | Cantidad (g/kg) |
|-----------|----------------------------|-----------------|
| 1         | Hidroxipropilmetilcelulosa | 50.00           |
| 2         | Polietilenglicol           | 7.50            |
| 3         | Metanol                    | 628.30          |
| 4         | Diclorometano              | 314.20          |

**CUADRO 14**

**Fórmula de la composición de recubrimiento entérico**

| No. serie | Ingrediente                                                                                     | Cantidad (g/kg) |
|-----------|-------------------------------------------------------------------------------------------------|-----------------|
| 1         | Copolímero de ácido metacrílico (copolímero de ácido metacrílico – metacrilato de metilo (1:2)) | 80.00           |
| 2         | Copolímero de ácido metacrílico (copolímero de ácido metacrílico – metacrilato de metilo (1:1)) | 6.4             |
| 3         | Citrato de trietilo                                                                             | 16.80           |
| 4         | Acetona                                                                                         | 297.90          |
| 5         | Alcohol isopropílico                                                                            | 515.60          |
| 6         | Agua purificada                                                                                 | 42.40           |
| 7         | Talco                                                                                           | 43.20           |

El procedimiento de fabricación fue similar al del ejemplo 1.

**EJEMPLO 5**

**CUADRO 15**

**Fórmula de núcleo de tableta**

| No. serie | Ingrediente                | Cantidad (mg/tab) |
|-----------|----------------------------|-------------------|
| 1         | Bicalutamida               | 70.00             |
| 2         | Lactosa monohidratada      | 39.92             |
| 3         | Polivinilpirrolidona       | 3.60              |
| 4         | Almidón glicolato de sodio | 6.00              |
| 5         | Estearato de magnesio      | 0.48              |

**CUADRO 16**

**Fórmula de composición de sub-recubrimiento**

| No. serie | Ingrediente                | Cantidad (g/kg) |
|-----------|----------------------------|-----------------|
| 1         | Hidroxipropilmetilcelulosa | 50.00           |
| 2         | Polietilenglicol           | 7.50            |
| 3         | Metanol                    | 628.30          |
| 4         | Diclorometano              | 314.20          |

**CUADRO 17**

**Fórmula de la composición de recubrimiento entérico**

| No. serie | Ingrediente                                                                                     | Cantidad (g/kg) |
|-----------|-------------------------------------------------------------------------------------------------|-----------------|
| 1         | Copolímero de ácido metacrílico (copolímero de ácido metacrílico – metacrilato de metilo (1:2)) | 80.00           |
| 2         | Copolímero de ácido metacrílico (copolímero de ácido metacrílico – metacrilato de metilo (1:1)) | 6.4             |
| 3         | Citrato de trietilo                                                                             | 16.80           |
| 4         | Acetona                                                                                         | 297.90          |
| 5         | Alcohol isopropílico                                                                            | 515.60          |
| 6         | Agua purificada                                                                                 | 42.40           |
| 7         | Talco                                                                                           | 43.20           |

La fórmula y el procedimiento fueron similares al ejemplo 1. Las tabletas que corresponden a una dosis total de 350 mg de bicalutamida (esto es, cinco tabletas recubiertas), se introdujeron en las cubiertas de una cápsula dura de gelatina.

**EJEMPLO 6**

**CUADRO 18**

**Fórmula de núcleo de tableta**

5

| No. serie | Ingrediente                | Cantidad (mg/tab) |
|-----------|----------------------------|-------------------|
| 1         | Bicalutamida               | 50.00             |
| 2         | Celulosa microcristalina   | 36.10             |
| 3         | Hidroxipropilmetilcelulosa | 60.00             |
| 4         | Almidón glicolato de sodio | 3.50              |
| 5         | Estearato de magnesio      | 0.40              |

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**CUADRO 19**

**Fórmula de composición de sub-recubrimiento**

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| No. serie | Ingrediente                | Cantidad (g/kg) |
|-----------|----------------------------|-----------------|
| 1         | Hidroxipropilmetilcelulosa | 50.00           |
| 2         | Polietilenglicol           | 7.50            |
| 3         | Metanol                    | 628.30          |
| 4         | Diclorometano              | 314.20          |

**CUADRO 20**

**Fórmula de la composición de recubrimiento entérico**

| No. serie | Ingrediente                                                                                     | Cantidad (g/kg) |
|-----------|-------------------------------------------------------------------------------------------------|-----------------|
| 1         | Copolímero de ácido metacrílico (copolímero de ácido metacrílico – metacrilato de metilo (1:2)) | 80.00           |
| 2         | Copolímero de ácido metacrílico (copolímero de ácido metacrílico – metacrilato de metilo (1:1)) | 6.4             |
| 3         | Citrato de trietilo                                                                             | 16.80           |
| 4         | Acetona                                                                                         | 297.90          |
| 5         | Alcohol isopropílico                                                                            | 515.60          |
| 6         | Agua purificada                                                                                 | 42.40           |
| 7         | Talco                                                                                           | 43.20           |

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La bicalutamida, la celulosa microcristalina y la hidroxipropilmetilcelulosa, se tamizaron y se mezclaron en las cantidades indicadas en el cuadro 18. La mezcla se mezcló con almidón glicolato de sodio y se lubricó con estearato de magnesio. La mezcla lubricada se comprimó en tabletas en una máquina rotativa de compresión de tabletas. Las tabletas se sometieron a un sub-recubrimiento y después a un recubrimiento entérico de acuerdo con el procedimiento de fabricación indicado en el ejemplo 1. Las tabletas que corresponden a una dosis total de 250 mg de bicalutamida (esto es, cinco tabletas recubiertas), se introdujeron en cubiertas de cápsula dura de gelatina.

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EJEMPLO 7

CUADRO 21

Fórmula de tableta de liberación inmediata

| No. serie | Ingrediente                | Cantidad (mg/tab) |
|-----------|----------------------------|-------------------|
| 1         | Bicalutamida               | 100.00            |
| 2         | Lactosa monohidratada      | 75.20             |
| 3         | Almidón glicolato de sodio | 14.00             |
| 4         | Polivinilpirrolidona       | 3.00              |
| 5         | Agua purificada            | c.s.              |
| 6         | Almidón glicolato de sodio | 7.00              |
| 7         | Estearato de magnesio      | 0.80              |

CUADRO 22

Fórmula de tableta de liberación sostenida

| No. serie | Ingrediente                | Cantidad (mg/tab) |
|-----------|----------------------------|-------------------|
| 1         | Bicalutamida               | 250.00            |
| 2         | Celulosa microcristalina   | 180.50            |
| 3         | Hidroxipropilmetilcelulosa | 300.00            |
| 4         | Almidón glicolato de sodio | 17.50             |
| 5         | Estearato de magnesio      | 2.00              |

Tableta de liberación inmediata: La bicalutamida, el almidón glicolato de sodio (porción intragranular) y la lactosa monohidratada se tamizaron y se mezclaron en las cantidades indicadas en el cuadro 20. La polivinilpirrolidona disuelta en una cantidad suficiente de agua purificada se usó para granular la mezcla de polvo seco. Esta mezcla se secó y se tamizó

para obtener gránulos secos. Entonces estos gránulos se mezclaron con la cantidad restante de almidón glicolato de sodio y el estearato de magnesio. La mezcla lubricada se comprimió en tabletas usando punzones redondos de 6 mm.

- 5                      Tableta de liberación sostenida: La bicalutamida, la celulosa microcristalina y la hidroxipropilmetilcelulosa se tamizaron y se mezclaron en las cantidades indicadas en el cuadro 22. Esta mezcla se mezcló con almidón glicolato de sodio y se lubricó con estearato de magnesio. La mezcla lubricada se comprimió en tabletas en una máquina rotativa de compresión de
- 10 tabletas. Las tabletas se sometieron a un sub-recubrimiento y después a un recubrimiento entérico de acuerdo con el procedimiento de fabricación indicado en el ejemplo 1. Las dos tabletas de este ejemplo se introdujeron en una cubierta de cápsula dura de gelatina.

## **NOVEDAD DE LA INVENCION**

### **REIVINDICACIONES**

5                    1.- Un método para producir un efecto antiandrogénico en un  
mamífero en necesidad del mismo, que comprende administrar al mamífero  
por vía oral una cantidad farmacéuticamente efectiva de bicalutamida en un  
programa de dosificación seleccionado del grupo de: dosificación tres veces a  
la semana, dosificación dos veces a la semana, y dosificación una vez a la  
10 semana.

2.- El método de conformidad con la reivindicación 1,  
caracterizado además porque comprende administrar al mamífero por vía oral  
una cantidad farmacéuticamente efectiva de bicalutamida en un programa de  
dosificación de una vez a la semana.

15                    3.- El método de conformidad con la reivindicación 1,  
caracterizado además porque la cantidad farmacéuticamente efectiva de  
bicalutamida varía de aproximadamente 150 mg a aproximadamente 1000  
mg.

20                    4.- Un método para producir un efecto antiandrogénico en un  
mamífero en necesidad del mismo, que comprende administrar al mamífero  
por vía oral una composición farmacéutica de liberación modificada de  
bicalutamida en un programa de dosificación de una vez a la semana.

5.- El método de conformidad con la reivindicación 4,

caracterizado además porque la composición farmacéutica de bicalutamida de liberación modificada se administra como una monoterapia.

6.- El método de conformidad con la reivindicación 4, caracterizado además porque la composición farmacéutica de bicalutamida de liberación modificada se administra como parte de una terapia de combinación.

7.- Una composición farmacéutica de bicalutamida de liberación modificada para producir un efecto antiandrogénico en un mamífero en necesidad del mismo, en donde la composición se administra en un programa de dosificación de una vez a la semana.

8.- La composición farmacéutica de liberación modificada de conformidad con la reivindicación 7, caracterizada además porque comprende bicalutamida en una escala de aproximadamente 50 mg a aproximadamente 1000 mg.

9.- La composición farmacéutica de liberación modificada de conformidad con la reivindicación 8, caracterizada además porque comprende bicalutamida en una escala de aproximadamente 150 mg a aproximadamente 600 mg.

10.- La composición farmacéutica de liberación modificada de conformidad con la reivindicación 7, caracterizada además porque se formula en forma de gránulos, tabletas, tabletas de capas, minitabledas, pellas o cápsulas.

11.- La composición farmacéutica de liberación modificada de

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conformidad con la reivindicación 7, caracterizada además porque la liberación modificada es una liberación controlada, liberación sostenida, liberación prolongada, liberación retardada, liberación impulsada, liberación doble, liberación cronometrada, o liberación específica de sitio.

5                   12.- La composición farmacéutica de liberación modificada de conformidad con la reivindicación 11, caracterizada además porque la liberación modificada es liberación retardada o liberación impulsada.

10                   13.- La composición farmacéutica de liberación modificada de conformidad con la reivindicación 7, caracterizada además porque es una composición de liberación impulsada oral que comprende por lo menos una tableta de liberación inmediata y por lo menos una tableta recubierta con polímeros de liberación retardada.

15                   14.- Una composición farmacéutica de bicalutamida de liberación modificada administrada en un programa de dosificación seleccionado del grupo de: dosificación tres veces a la semana, dosificación dos veces a la semana, y dosificación una vez a la semana

15.- Un equipo que comprende una composición farmacéutica de bicalutamida de liberación modificada para administración oral en un programa de dosificación de una vez a la semana.

20                   16.- El equipo de conformidad con la reivindicación 15, caracterizado además porque la composición farmacéutica de liberación modificada se administra una vez al día hasta un máximo de cuatro semanas, como dosis de carga, seguido por la administración semanal de la misma

composición como dosis de mantenimiento.

17.- El equipo de conformidad con la reivindicación 15, caracterizado además porque la composición farmacéutica de liberación modificada se administra una vez al día como dosis de carga hasta alcanzar  
5 una concentración plasmática de estado estable de bicalutamida, seguido por la administración semanal de la misma composición como dosis de mantenimiento.

18.- Una composición farmacéutica de bicalutamida de liberación modificada que es una composición de liberación impulsada oral formulada  
10 como una combinación de componentes de liberación inmediata y liberación retardada, que comprende bicalutamida en una cantidad de aproximadamente 20% a aproximadamente 80% de la dosis total en el componente de liberación inmediata, y en una cantidad de aproximadamente 80% a aproximadamente 20% de la dosis total en el componente de liberación retardada.

15 19.- La composición farmacéutica de liberación modificada de conformidad con la reivindicación 18, caracterizada además porque la composición de liberación impulsada oral comprende por lo menos una tableta de liberación inmediata y por lo menos una tableta recubierta con polímeros de liberación retardada, en donde la composición exhibe biodisponibilidad  
20 mejorada en comparación con una composición convencional de bicalutamida.

20.- Una composición farmacéutica de bicalutamida de liberación modificada que tiene biodisponibilidad mejorada y comprende uno o más excipientes, o mezclas de los mismos, que prolongan la vida media de la

bicalutamida.

21.- La composición farmacéutica de liberación modificada de conformidad con la reivindicación 20, caracterizada además porque los excipientes incluyen polímeros que modifican la velocidad y tiempo de liberación de la bicalutamida, seleccionados del grupo de celulosas, polímeros de vinilpirrolidona, homopolímeros de óxido de alquileo, polímeros superdesintegrantes, polímeros de ácido acrílico y gomas de origen vegetal, animal, mineral o sintético.

22.- La composición farmacéutica de liberación modificada de conformidad con la reivindicación 21, caracterizada además porque los polímeros son polímeros entéricos tales como ésteres de celulosa y sus derivados, polímeros y copolímeros de vinilo, copolímeros de ácido metacrílico sensibles al pH, goma laca, etcétera.

23.- Una composición farmacéutica de bicalutamida de liberación modificada que libera la bicalutamida de acuerdo con el siguiente perfil de disolución: se libera entre 20% y 65% de bicalutamida en fluido gástrico simulado; se libera entre 40% y 75% en amortiguador de pH 4.5; y se libera no menos de 60% en fluido intestinal simulado, cuando se prueba en el aparato USP de tipo 1 usando el método de cambio de pH, con fluido gástrico simulado de pH 1.2, amortiguador de pH 4.5, y fluido intestinal simulado de pH 6.8, y en donde el medio de disolución comprende 1% de laurilsulfato de sodio.

24.- La composición farmacéutica de liberación modificada de

conformidad con la reivindicación 23, caracterizada además porque las pruebas de disolución se efectúan en fluido gástrico simulado durante 2 horas aproximadamente, en amortiguador de pH 4.5 durante 2 horas aproximadamente, y en fluido intestinal simulado de pH 6.8 durante el periodo

5 restante.

**RESUMEN DE LA INVENCION**

La invención se refiere a una formulación oral que contiene bicalutamida con un patrón de liberación modificada; la composición es adecuada para ser administrada en un programa de dosificación de tres veces a la semana, dos veces a la semana y una vez a la semana; la composición se usa para producir un efecto antiandrogénico.

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EA

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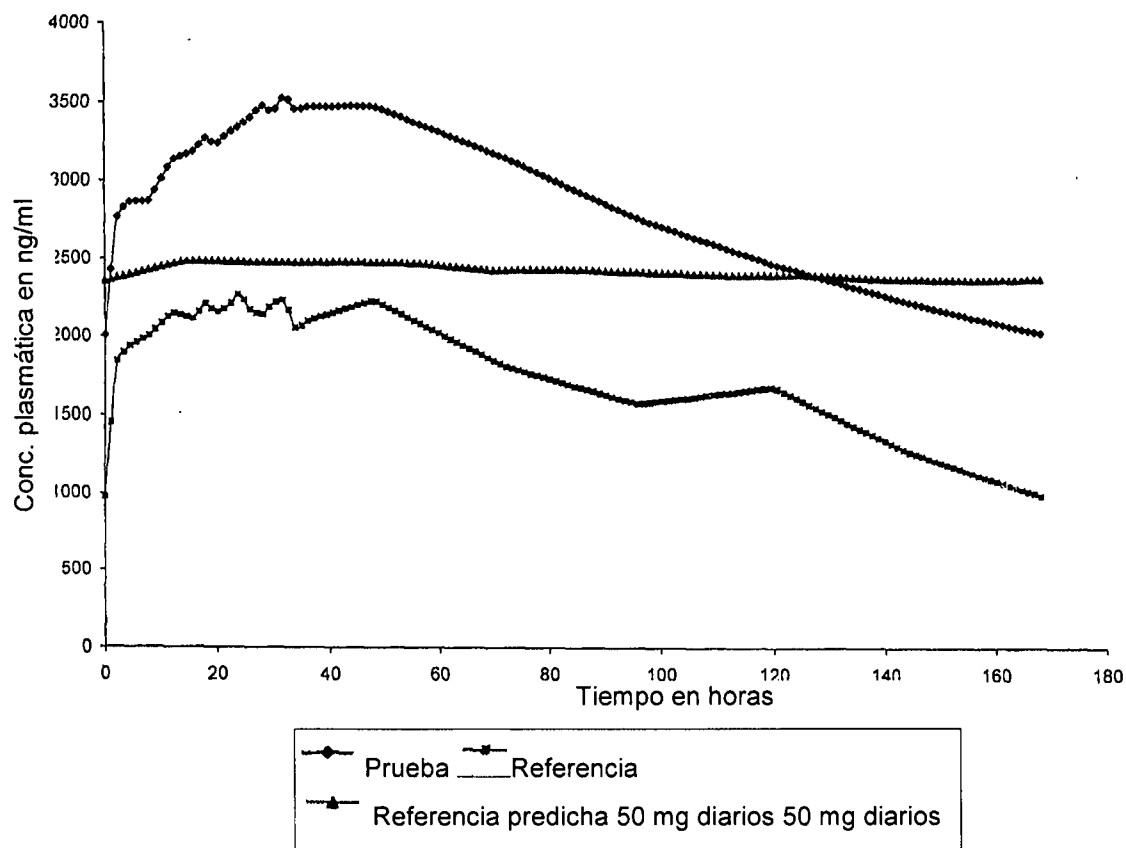


FIG. 1

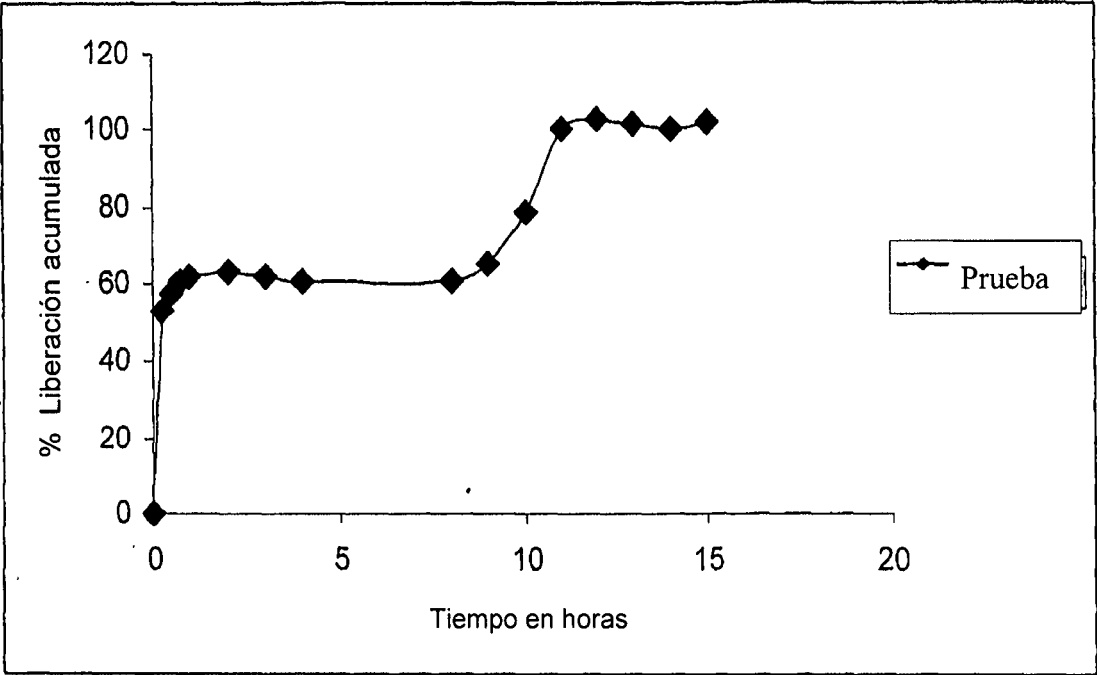


FIG. 2

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

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

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

In relation to this international application No. PCT/

PANACEA BIOTEC LIMITED is entitled to apply for and be granted a patent by virtue of the following:

(ii) PANACEA BIOTEC LIMITED is entitled as employer of the inventors SINGH, Amarjit; SINGH, Sarabjit and PUTHLI, Shivanand.

(iv) an assignment from SINGH, Amarjit, SINGH, Sarabjit and PUTHLI, Shivanand to PANACEA BIOTEC LIMITED, by an IP Assignment agreement dated 10 June 2006, having effect from the date of creation of the invention.

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

**Box No. VIII (iii) DECLARATION: ENTITLEMENT TO CLAIM PRIORITY**

*The declaration must conform to the standardized wording provided for in Section 213; see Notes to Boxes Nos. VIII, VIII (i) to (v) (in general) and the specific Notes to Box No. VIII (iii). If this Box is not used, this sheet should not be included in the request.*

Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application specified below, where the applicant is not the applicant who filed the earlier application or where the applicant's name has changed since the filing of the earlier application (Rules 4.17(iii) and 51bis.1(a)(iii)):

in relation to this international application [No. PCT/.....],

PANACEA BIOTEC LIMITED, is entitled to claim priority of earlier application No. 1074/MUM/2006 by virtue of the following:

(i) the applicant is the inventor of the subject matter for which protection was sought by way of the earlier application.

(ii) PANACEA BIOTEC LIMITED, is entitled as employer of the inventors :  
SINGH Amarjit, SINGH Sarabjit and PUTHLI Shivanand

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

**Box No. VIII (iv) DECLARATION: INVENTORSHIP (only for the purposes of the designation of the United States of America)**  
*The declaration must conform to the following standardized wording provided for in Section 214; see Notes to Boxes Nos. VIII, VIII (i) to (v) (in general) and the specific Notes to Box No. VIII (iv). If this Box is not used, this sheet should not be included in the request.*

**Declaration of inventorship (Rules 4.17(iv) and 51bis.1(a)(iv))  
for the purposes of the designation of the United States of America:**

I hereby declare that I believe I am the original, first and sole (if only one inventor is listed below) or joint (if more than one inventor is listed below) inventor of the subject matter which is claimed and for which a patent is sought.

This declaration is directed to the international application of which it forms a part (if filing declaration with application).

This declaration is directed to international application No. PCT/..... (if furnishing declaration pursuant to Rule 26ter).

I hereby declare that my residence, mailing address, and citizenship are as stated next to my name.

I hereby state that I have reviewed and understand the contents of the above-identified international application, including the claims of said application. I have identified in the request of said application, in compliance with PCT Rule 4.10, any claim to foreign priority, and I have identified below, under the heading "Prior Applications," by application number, country or Member of the World Trade Organization, day, month and year of filing, any application for a patent or inventor's certificate filed in a country other than the United States of America, including any PCT international application designating at least one country other than the United States of America, having a filing date before that of the application on which foreign priority is claimed.

Prior Applications: . Application No. 1074/MUM/2006 dated July 07, 2006 filed in India. ....

I hereby acknowledge the duty to disclose information that is known by me to be material to patentability as defined by 37 C.F.R. § 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the PCT international filing date of the continuation-in-part application.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name: . SINGH, Amarjit .....

Residence: . Mumbai India .....  
(city and either US state, if applicable, or country)

Mailing Address: . 201, Samarpan Complex, New Link Road, Chakala, Andheri (E), Mumbai - 400099, .....  
Maharashtra, INDIA

Citizenship: . Indian .....

Inventor's Signature: . *A Singh* ..... Date: . 5<sup>th</sup> July 2007 .....  
(The signature must be that of the inventor, not that of the agent)

Name: . SINGH, Sarabjit .....

Residence: . Mumbai India .....  
(city and either US state, if applicable, or country)

Mailing Address: . 201, Samarpan Complex, New Link Road, Chakala, Andheri (E), Mumbai - 400099, .....  
Maharashtra, INDIA

Citizenship: . Indian .....

Inventor's Signature: . *Sarabjit Singh* ..... Date: . 5<sup>th</sup> July 2007 .....  
(The signature must be that of the inventor, not that of the agent)

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

**Continuation of Box No. VIII (i) to (v) DECLARATION**

*If the space is insufficient in any of Boxes Nos. VIII (i) to (v) to furnish all the information, including in the case where more than two inventors are to be named in Box No. VIII (iv), in such case, write "Continuation of Box No. VIII ..." (indicate the item number of the Box) and furnish the information in the same manner as required for the purposes of the Box in which the space was insufficient. If additional space is needed in respect of two or more declarations, a separate continuation box must be used for each such declaration. If this Box is not used, this sheet should not be included in the request.*

Name: .PUTHLI, Shivanand

Residence: Mumbai, India  
(city and either US state, if applicable, or country)

Mailing Address: 201, Samarpan Complex, New Link Road, Chakala, Andheri (E),  
Mumbai - 400099, Maharashtra, INDIA

Citizenship: Indian

Inventor's Signature: ..... S. P. Puthli ..... Date: ... 5<sup>th</sup> July 2007 .....  
(The signature must be that of the inventor, not that of the agent)

85

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/ AT

# 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.

For International Preliminary Examining Authority use only

|                                                                                                                                                                                                                                                                                                        |                                                                          |                                                                           |  |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|---------------------------------------------------------------------------|--|
| Identification of IPEA                                                                                                                                                                                                                                                                                 |                                                                          | Date of receipt of DEMAND                                                 |  |
| <b>Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION</b>                                                                                                                                                                                                                                       |                                                                          | Applicant's or agent's file reference<br>GRDBCL_01                        |  |
| International application No.<br>PCT/IN07/00274                                                                                                                                                                                                                                                        | International filing date (day/month/year)<br>05 JULY 2007<br>(05.07.07) | (Earliest) Priority date (day/month/year)<br>07 JULY 2006<br>(07.07.2006) |  |
| Title of invention<br>METHODS AND COMPOSITIONS FOR PRODUCING ANTI-ANDROGENIC EFFECTS                                                                                                                                                                                                                   |                                                                          |                                                                           |  |
| <b>Box No. II APPLICANT(S)</b>                                                                                                                                                                                                                                                                         |                                                                          |                                                                           |  |
| 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.)<br>Panacea Biotech Limited.<br>201, Samarpan Complex,<br>New-Link Road, Chakala,<br>Andheri (E), Mumbai 400099,<br>Maharashtra, India |                                                                          | Telephone No.<br>91 22 28261113                                           |  |
|                                                                                                                                                                                                                                                                                                        |                                                                          | Facsimile No.<br>91 22 28386955                                           |  |
|                                                                                                                                                                                                                                                                                                        |                                                                          | Applicant's registration No. with the Office                              |  |
| State (that is, country) of nationality:<br>IN                                                                                                                                                                                                                                                         |                                                                          | State (that is, country) of residence:<br>IN                              |  |
| 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.)<br>SINGH, Amarjit<br>201, Samarpan Complex,<br>New-Link Road, Chakala,<br>Andheri (E), Mumbai 400099,<br>Maharashtra, India           |                                                                          |                                                                           |  |
| State (that is, country) of nationality:<br>IN                                                                                                                                                                                                                                                         |                                                                          | State (that is, country) of residence:<br>IN                              |  |
| <input checked="" type="checkbox"/> Further applicants are indicated on a continuation sheet.                                                                                                                                                                                                          |                                                                          |                                                                           |  |

Sheet No. 2

International application No.  
PCT/IN07/00274

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.)  
SINGH, Sarabjit  
201, Samarpan Complex,  
New-Link Road, Chakala,  
Andheri (E), Mumbai 400099,  
Maharashtra, India

State (that is, country) of nationality:  
IN

State (that is, country) of residence:  
IN

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.)  
PUTHLI, Shivanand  
201, Samarpan Complex,  
New-Link Road, Chakala,  
Andheri (E), Mumbai 400099,  
Maharashtra, India

State (that is, country) of nationality:  
IN

State (that is, country) of residence:  
IN

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. 3

International application No.  
PCT/IN07/00274

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.)

Andheria, Mahalaxmi Ph.D  
Panacea Biotec Limited.  
201, Samarpan Complex,  
New-Link Road, Chakala,  
Andheri (E), Mumbai 400099,  
Maharashtra, India

Telephone No.

91 22 28261113

Facsimile No.

91 22 28386955

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. ☐ Where the IPEA wishes to start the international preliminary examination at the same time as the international search in accordance with Rule 69.1(b), the applicant requests the IPEA to postpone the start of the international preliminary examination until the expiration of the applicable time limit under Rule 69.1(d).

4. ☐ The applicant expressly wishes the international preliminary examination to start earlier than at the expiration of the applicable time limit under Rule 54bis.1(a).

\* 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 filing of this demand constitutes the election of all Contracting States which are designated and are bound by Chapter II of the PCT.

Sheet No. 4

International application No.  
PCT/IN07/00274

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                                                                | : | 1 sheets |
| 6. other (specify)                                                       | : | sheets   |

For International Preliminary Examining Authority use only

- | received                 | not received             |
|--------------------------|--------------------------|
| <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | <input type="checkbox"/> |
| <input type="checkbox"/> | <input type="checkbox"/> |

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

- |                                                                                          |                                                                                     |
|------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| 1. <input checked="" type="checkbox"/> fee calculation sheet                             | 5. <input type="checkbox"/> statement explaining lack of signature                  |
| 2. <input type="checkbox"/> original separate power of attorney                          | 6. <input type="checkbox"/> sequence listing in electronic form                     |
| 3. <input type="checkbox"/> original general power of attorney                           | 7. <input type="checkbox"/> tables in electronic form related to a sequence listing |
| 4. <input type="checkbox"/> copy of general power of attorney; reference number, if any: | 8. <input type="checkbox"/> other (specify):                                        |

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).

ASINGH

SINGH, AMARJIT  
APPLICANT

Sarabjit Singh  
SINGH, SARABJIT  
APPLICANT

S.P. Puthli

PUTHLI, SHIVANAND  
APPLICANT

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 time limit 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.

6. ☐ The date of receipt of the demand is AFTER the expiration of the time limit under Rule 54bis.1(a) and item 7 or 8, below, does not apply.
7. ☐ The date of receipt of the demand is WITHIN the time limit under Rule 54bis.1(a) as extended by virtue of Rule 80.5.
8. ☐ Although the date of receipt of the demand is after the expiration of the time limit under Rule 54bis.1(a), the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

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.                                                 |  |
| International Filing Date                                                     |  |
| Name of receiving Office and "PCT International Application"                  |  |
| Applicant's or agent's file reference<br>(if desired) (12 characters maximum) |  |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                         |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Box No. I TITLE OF INVENTION<br>METHODS AND COMPOSITIONS FOR PRODUCING ANTI-ANDROGENIC EFFECTS                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                         |
| Box No. II APPLICANT <input type="checkbox"/> 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.)<br>Panacea Biotec Limited.<br>201, Samarpan Complex,<br>New-Link Road, Chakala,<br>Andheri (E), Mumbai 400099,<br>Maharashtra, India | Telephone No.<br>91 22 28261113<br>Facsimile No.<br>91 22 28386955<br>Teleprinter No.<br>Applicant's registration No. with the Office                                                                                                                                   |
| State (that is, country) of nationality:<br>IN                                                                                                                                                                                                                                                                                                                                                                                                              | State (that is, country) of residence:<br>IN                                                                                                                                                                                                                            |
| This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input checked="" type="checkbox"/> all designated States except the United States of America <input type="checkbox"/> the United States of America only <input type="checkbox"/> 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.)<br>SINGH, Amarjit<br>201, Samarpan Complex,<br>New-Link Road, Chakala,<br>Andheri (E), Mumbai 400099,<br>Maharashtra, INDIA         | This person is:<br><input type="checkbox"/> applicant only<br><input checked="" type="checkbox"/> applicant and inventor<br><input type="checkbox"/> inventor only (If this check-box is marked, do not fill in below.)<br>Applicant's registration No. with the Office |
| State (that is, country) of nationality:<br>IN                                                                                                                                                                                                                                                                                                                                                                                                              | State (that is, country) of residence:<br>IN                                                                                                                                                                                                                            |
| This person is applicant for the purposes of: <input type="checkbox"/> all designated States <input type="checkbox"/> all designated States except the United States of America <input checked="" type="checkbox"/> the United States of America only <input type="checkbox"/> the States indicated in the Supplemental Box                                                                                                                                 |                                                                                                                                                                                                                                                                         |
| <input checked="" type="checkbox"/> 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: <input type="checkbox"/> agent <input type="checkbox"/> 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.)<br>ANDHERIA, Mahalaxmi<br>Panacea Biotec Limited.<br>201, Samarpan Complex,<br>New-Link Road, Chakala,<br>Andheri (E), Mumbai 400099,<br>Maharashtra, INDIA.                                                                                                                               | Telephone No.<br>91 22 28261113<br>Facsimile No.<br>91 22 28386955<br>Teleprinter No.<br>Agent's registration No. with the Office                                                                                                                                       |
| <input checked="" type="checkbox"/> Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                         |

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

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

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>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.)</p> <p>SINGH, Sarabjit<br/>201, Samarpan Complex,<br/>New-Link Road, Chakala,<br/>Andheri (E), Mumbai 400099,<br/>Maharashtra, INDIA</p> | <p>This person is:</p> <p><input type="checkbox"/> applicant only</p> <p><input checked="" type="checkbox"/> applicant and inventor</p> <p><input type="checkbox"/> inventor only (If this check-box is marked, do not fill in below.)</p> <p>Applicant's registration No. with the Office</p> |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

|                                                |                                              |
|------------------------------------------------|----------------------------------------------|
| State (that is, country) of nationality:<br>IN | State (that is, country) of residence:<br>IN |
|------------------------------------------------|----------------------------------------------|

|                                                                                                                                                                                                                                                                                                                                                                |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>This person is applicant for the purposes of:</p> <p><input type="checkbox"/> all designated States</p> <p><input type="checkbox"/> all designated States except the United States of America</p> <p><input checked="" type="checkbox"/> the United States of America only</p> <p><input type="checkbox"/> the States indicated in the Supplemental Box</p> |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                                                                                                                                |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>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.)</p> <p>PUTHLI, Shivanand<br/>201, Samarpan Complex,<br/>New-Link Road, Chakala,<br/>Andheri (E), Mumbai 400099,<br/>Maharashtra, INDIA</p> | <p>This person is:</p> <p><input type="checkbox"/> applicant only</p> <p><input checked="" type="checkbox"/> applicant and inventor</p> <p><input type="checkbox"/> inventor only (If this check-box is marked, do not fill in below.)</p> <p>Applicant's registration No. with the Office</p> |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

|                                                |                                              |
|------------------------------------------------|----------------------------------------------|
| State (that is, country) of nationality:<br>IN | State (that is, country) of residence:<br>IN |
|------------------------------------------------|----------------------------------------------|

|                                                                                                                                                                                                                                                                                                                                                                |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>This person is applicant for the purposes of:</p> <p><input type="checkbox"/> all designated States</p> <p><input type="checkbox"/> all designated States except the United States of America</p> <p><input checked="" type="checkbox"/> the United States of America only</p> <p><input type="checkbox"/> the States indicated in the Supplemental Box</p> |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

|                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                     |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>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.)</p> | <p>This person is:</p> <p><input type="checkbox"/> applicant only</p> <p><input type="checkbox"/> applicant and inventor</p> <p><input type="checkbox"/> inventor only (If this check-box is marked, do not fill in below.)</p> <p>Applicant's registration No. with the Office</p> |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

|                                          |                                        |
|------------------------------------------|----------------------------------------|
| State (that is, country) of nationality: | State (that is, country) of residence: |
|------------------------------------------|----------------------------------------|

|                                                                                                                                                                                                                                                                                                                                                     |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>This person is applicant for the purposes of:</p> <p><input type="checkbox"/> all designated States</p> <p><input type="checkbox"/> all designated States except the United States of America</p> <p><input type="checkbox"/> the United States of America only</p> <p><input type="checkbox"/> the States indicated in the Supplemental Box</p> |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

|                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                     |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>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.)</p> | <p>This person is:</p> <p><input type="checkbox"/> applicant only</p> <p><input type="checkbox"/> applicant and inventor</p> <p><input type="checkbox"/> inventor only (If this check-box is marked, do not fill in below.)</p> <p>Applicant's registration No. with the Office</p> |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

|                                          |                                        |
|------------------------------------------|----------------------------------------|
| State (that is, country) of nationality: | State (that is, country) of residence: |
|------------------------------------------|----------------------------------------|

|                                                                                                                                                                                                                                                                                                                                                     |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>This person is applicant for the purposes of:</p> <p><input type="checkbox"/> all designated States</p> <p><input type="checkbox"/> all designated States except the United States of America</p> <p><input type="checkbox"/> the United States of America only</p> <p><input type="checkbox"/> the States indicated in the Supplemental Box</p> |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

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

Box No. V DESIGNATIONS

The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents. However,

- ☐ DE Germany is not designated for any kind of national protection
- ☐ JP Japan is not designated for any kind of national protection
- ☐ KR Republic of Korea is not designated for any kind of national protection
- ☐ RU Russian Federation is not designated for any kind of national protection

(The check-boxes above may only be used to exclude (irrevocably) the designations concerned if, at the time of filing, the international application contains in Box No. VI a priority claim to an earlier national application filed in the particular State concerned, in order to avoid the ceasing of the effect, under the national law, of this earlier national application. See the Notes to Box No. V as to the consequences of such national law provisions in these States.)

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 or Member of WTO | regional application: regional Office | international application: receiving Office |
| item (1)<br>07 July 2006<br>(07.07.2006)            | 1074/MUM/2006                 | IN                                             |                                       |                                             |
| item (2)                                            |                               |                                                |                                       |                                             |
| item (3)                                            |                               |                                                |                                       |                                             |

☐ 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) ☐ 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 4.1(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 / AT

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 |
|--------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|------------------------|
| <input type="checkbox"/> Box No. VIII (i)              | Declaration as to the identity of the inventor                                                                                       |                        |
| <input checked="" type="checkbox"/> Box No. VIII (ii)  | Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent             | 1                      |
| <input checked="" type="checkbox"/> 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 | 1                      |
| <input checked="" type="checkbox"/> Box No. VIII (iv)  | Declaration of inventorship (only for the purposes of the designation of the United States of America)                               | 1                      |
| <input type="checkbox"/> Box No. VIII (v)              | Declaration as to non-prejudicial disclosures or exceptions to lack of novelty                                                       |                        |

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

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

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

In relation to this international application No. PCT/

PANACEA BIOTEC LIMITED is entitled to apply for and be granted a patent by virtue of the following:

(ii) PANACEA BIOTEC LIMITED is entitled as employer of the inventors SINGH, Amarjit; SINGH, Sarabjit and PUTHLI, Shivanand.

(iv) an assignment from SINGH, Amarjit, SINGH, Sarabjit and PUTHLI, Shivanand to PANACEA BIOTEC LIMITED, by an IP Assignment agreement dated 10 June 2006, having effect from the date of creation of the invention.

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

**Box No. VIII (iii) DECLARATION: ENTITLEMENT TO CLAIM PRIORITY**

*The declaration must conform to the standardized wording provided for in Section 213, see Notes to Boxes Nos. VIII, VIII (i) to (v) in general and the specific Notes to Box No. VIII (iii). If this Box is not used, this sheet should not be included in the request.*

Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application specified below, where the applicant is not the applicant who filed the earlier application or where the applicant's name has changed since the filing of the earlier application (Rules 4.17(iii) and 51bis.1(a)(iii)):

in relation to this international application [No. PCT/.....],

PANACEA BIOTEC LIMITED, is entitled to claim priority of earlier application No 1074/MUM/2006 by virtue of the following:

(i) the applicant is the inventor of the subject matter for which protection was sought by way of the earlier application.

(ii) PANACEA BIOTEC LIMITED, is entitled as employer of the inventors SINGH Amarjit, SINGH Sarabjit and PUTHLI Shivanand

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

Box No. VIII (iv) **DECLARATION: INVENTORSHIP** (only for the purposes of the designation of the United States of America)  
*The declaration must conform to the following standardized wording provided for in Section 214; see Notes to Boxes Nos. VIII, VIII (iv) (v) (in general) and the specific Notes to Box No. VIII (iv). If this Box is not used, this sheet should not be included in the request.*

**Declaration of inventorship (Rules 4.17(iv) and 51bis.1(a)(iv))  
for the purposes of the designation of the United States of America:**

I hereby declare that I believe I am the original, first and sole (if only one inventor is listed below) or joint (if more than one inventor is listed below) inventor of the subject matter which is claimed and for which a patent is sought.

This declaration is directed to the international application of which it forms a part (if filing declaration with application)

This declaration is directed to international application No. PCT/..... (if furnishing declaration pursuant to Rule 26ter)

I hereby declare that my residence, mailing address, and citizenship are as stated next to my name

I hereby state that I have reviewed and understand the contents of the above-identified international application, including the claims of said application. I have identified in the request of said application, in compliance with PCT Rule 4.10, any claim to foreign priority, and I have identified below, under the heading "Prior Applications," by application number, country or Member of the World Trade Organization, day, month and year of filing, any application for a patent or inventor's certificate filed in a country other than the United States of America, including any PCT international application designating at least one country other than the United States of America, having a filing date before that of the application on which foreign priority is claimed.

Prior Applications: Application No. 1074/MUM/2006, dated July 07, 2006 filed in India, ...

I hereby acknowledge the duty to disclose information that is known by me to be material to patentability as defined by 37 C.F.R. § 1.56, including for continuation-in-part applications, material information which became available between the filing date of the prior application and the PCT international filing date of the continuation-in-part application.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon

Name: SINGH, Amarjit

Residence: Mumbai India  
(city and either US state, if applicable, or country)

Mailing Address: 201, Samarpan Complex, New Link Road, Chakala, Andheri (E), Mumbai - 400099,  
Maharashtra, INDIA

Citizenship: Indian

Inventor's Signature: *A Singh* Date: 5<sup>th</sup> July 2007

(The signature must be that of the inventor, not that of the agent)

Name: SINGH, Sarabjit

Residence: Mumbai India  
(city and either US state, if applicable, or country)

Mailing Address: 201, Samarpan Complex, New Link Road, Chakala, Andheri (E), Mumbai - 400099,  
Maharashtra, INDIA

Citizenship: Indian

Inventor's Signature: *Sarabjit Singh* Date: 5<sup>th</sup> July 2007

(The signature must be that of the inventor, not that of the agent)

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

2/5

Sheet No. 7

Continuation of Box No. VIII (i) to (v) DECLARATION

If the space is insufficient in any of Boxes Nos. VIII (i) to (v) to furnish all the information, including in the case where more than two inventors are to be named in Box No. VIII (iv), in such case, write "Continuation of Box No. VIII" (indicate the item number of the Box) and furnish the information in the same manner as required for the purposes of the Box in which the space was insufficient. If additional space is needed in respect of two or more declarations, a separate continuation box must be used for each such declaration. If this Box is not used, this sheet should not be included in the request.

Name: .PUTHLI, Shivanand

Residence: Mumbai, India  
(city and either US state, if applicable, or country)

Mailing Address: 201, Samarpan Complex, New Link Road, Chakala, Andheri (E),  
Mumbai - 400099, Maharashtra, INDIA

Citizenship: Indian

Inventor's Signature: S. P. Puthli Date: 5<sup>th</sup> July 2007  
(The signature must be that of the inventor, not that of the agent)

Box No. IX CHECK LIST: LANGUAGE OF FILING

| This international application contains                                                                            | This international application is accompanied by the following item(s) (mark the applicable check-boxes below and indicate in right column the number of each item)                                                           | Number of items |
|--------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------|
| (a) on paper, the following number of sheets                                                                       | 1. <input checked="" type="checkbox"/> fee calculation sheet                                                                                                                                                                  |                 |
| request (including declaration sheets) :                                                                           | 2. <input type="checkbox"/> original separate power of attorney                                                                                                                                                               |                 |
| description (excluding sequence listing and/or tables related thereto) :                                           | 3. <input type="checkbox"/> original general power of attorney                                                                                                                                                                |                 |
| claims :                                                                                                           | 4. <input type="checkbox"/> copy of general power of attorney; reference number, if any: .....                                                                                                                                |                 |
| abstract :                                                                                                         | 5. <input type="checkbox"/> statement explaining lack of signature                                                                                                                                                            |                 |
| drawings :                                                                                                         | 6. <input type="checkbox"/> priority document(s) identified in Box No. VI as item(s): .....                                                                                                                                   |                 |
| Sub-total number of sheets                                                                                         | 7. <input type="checkbox"/> translation of international application into (language): .....                                                                                                                                   |                 |
| sequence listing                                                                                                   | 8. <input type="checkbox"/> separate indications concerning deposited microorganism or other biological material                                                                                                              |                 |
| tables related thereto                                                                                             | 9. <input type="checkbox"/> sequence listing in electronic form (indicate type and number of carriers)                                                                                                                        |                 |
| (for both, actual number of sheets if filed on paper, whether or not also filed in electronic form, see (c) below) | (i) <input type="checkbox"/> copy submitted for the purposes of international search under Rule 13ter only (and not as part of the international application)                                                                 |                 |
| Total number of sheets                                                                                             | (ii) <input type="checkbox"/> (only where check-box (b)(i) or (c)(i) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Rule 13ter              |                 |
| 33                                                                                                                 | (iii) <input type="checkbox"/> together with relevant statement as to the identity of the copy or copies with the sequence listing mentioned in left column                                                                   |                 |
| (b) <input type="checkbox"/> only in electronic form (Section 801(a)(i))                                           | 10. <input type="checkbox"/> tables in electronic form related to sequence listing (indicate type and number of carriers)                                                                                                     |                 |
| (i) <input type="checkbox"/> sequence listing                                                                      | (i) <input type="checkbox"/> copy submitted for the purposes of international search under Section 802(b-quater) only (and not as part of the international application)                                                      |                 |
| (ii) <input type="checkbox"/> tables related thereto                                                               | (ii) <input type="checkbox"/> (only where check-box (b)(ii) or (c)(ii) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Section 802(b-quater) |                 |
| (c) <input type="checkbox"/> also in electronic form (Section 801(a)(ii))                                          | (iii) <input type="checkbox"/> together with relevant statement as to the identity of the copy or copies with the tables mentioned in left column                                                                             |                 |
| (i) <input type="checkbox"/> sequence listing                                                                      | 11. <input type="checkbox"/> other (specify): .....                                                                                                                                                                           |                 |
| (ii) <input type="checkbox"/> tables related thereto                                                               |                                                                                                                                                                                                                               |                 |
| Type and number of carriers (diskette, CD-ROM, CD-R or other) on which are contained the                           |                                                                                                                                                                                                                               |                 |
| <input type="checkbox"/> sequence listing: .....                                                                   |                                                                                                                                                                                                                               |                 |
| <input type="checkbox"/> tables related thereto: .....                                                             |                                                                                                                                                                                                                               |                 |
| (additional copies to be indicated under items 9(ii) and/or 10(ii), in right column)                               |                                                                                                                                                                                                                               |                 |

Figure of the drawings which should accompany the abstract:

Language of filing of the international application:

English

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

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

ASingh

SINGH, AMARJIT  
APPLICANT

Sarabjit Singh

SINGH, SARABJIT  
APPLICANT

S. I. Puthli

PUTHLI, SHIVANAND  
APPLICANT

| For receiving Office use only                                                                                                               |                                                                                         |
|---------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| 1. Date of actual receipt of the purported international application:                                                                       | 2. Drawings<br><input type="checkbox"/> received                                        |
| 3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application: | <input type="checkbox"/> not received                                                   |
| 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. <input type="checkbox"/> 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:

No.03/2008

**CONSULADO DE COLOMBIA  
NUEVA DELHI**

LA SUSCRITA, ENCARGADA DE LAS  
FUNCIONES CONSULARES ANTE LA EMBAJADA DE COLOMBIA EN NUEVA  
DELHI, INDIA,  
VISTOS LOS DOCUMENTOS PRESENTADOS POR LOS INTERESADOS

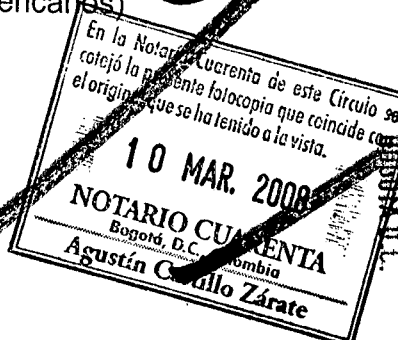
**CERTIFICA:**

QUE EL SEÑOR G. HARSHAPPAN, OFICIAL REGIONAL (OI) DEL MINISTERIO DE RELACIONES EXTERIORES DE INDIA, QUIEN AUTENTICO LA FIRMA DEL SEÑOR P.S. PANWAR DE LA EMPRESA PANACEA BIOTEC, FIRMANTE DEL PRESENTE DOCUMENTO, EJERCA EN LA FECHA LAS FUNCIONES INDICADAS Y SU FIRMA CORRESPONDE A LA REGISTRADA EN ESTE CONSULADO; QUE LA EMPRESA PANACEA BIOTEC, ESTA CONSTITUIDA DE ACUERDO CON LAS LEYES DE INDIA Y CUMPLE SU OBJETO CONFORME A LAS MISMAS (SEGÚN DECLARACION NOTARIADA ADJUNTA AL DOCUMENTO) DOMICILIADA EN NUEVA DELHI, INDIA; QUE EL SEÑOR P.S. PANWAR DE LA EMPRESA ARRIBA MENCIONADA, ESTA FACULTADO PARA FIRMAR EL PRESENTE DOCUMENTO.

DADO EN NUEVA DELHI A LOS ONCE DIAS (11) DEL MES DE ENERO DE DOS MIL OCHO (2008).

  
**OLYMPIA LEON DE SINGH**  
E.F.C.

PAGADO IMPUESTO DE TIMBRE Y  
DERECHOS CONSULARES: US \$110.00  
(Ciento nueve Dólares Americanos)



3, Palam Marg, First Floor, Vasant Vihar, New Delhi -110057 INDIA  
Tel.: 91-11-51-66-21-03, 51-66-21-05 Fax: 91-11-51-66-21-04, 51-66-21-08  
e-mail: emcolin@bol.net.in

PODER

Yo (nosotros), Panacea Biotec Ltd.

domiciliado(s) en, B-1 Extn./A-27, Mohan Co-operative Industrial Estate, Mathura Road, New Delhi - 110 044 - INDIA

Nombro(amos) a: JUAN PABLO CADENA SARMIENTO y/o CARLOS H. PALACIO EASTMAN y/o MARTIN E. TORRES CARDOZO, de Bogotá, Colombia, apoderados verdaderos y legales con poder especial amplio y suficiente, para recabar de las oficinas y autoridades colombianas administrativas, judiciales y de policía, en cualquier instancia o recurso, la obtención de patentes de invención, registros de marcas, diseños industriales, modelos de utilidad, depósitos de nombres comerciales, lemas comerciales y enseññas, registros de derechos de autor y contratos sobre los mismos, obtención de certificados de obtentor de variedades vegetales, así como sus prórrogas, renovaciones, anotaciones de traspaso, cambios de nombre, domicilio y/o dirección; elaborar, tramitar y registrar contratos de licencia y licencias de cualesquiera clases; intervenir como demandante o como demandado en cualquier instancia y recurso ante cualquier juez, corporación, funcionario público o autoridad en acciones judiciales, administrativas y de policía tales como: oposiciones al registro de marcas; acciones de caducidad, cancelación y nulidad; acciones reivindicatorias, acciones derivadas de la obtención o explotación de licencias; acciones de competencia desleal; demandas penales; acciones de indemnización de perjuicios, reclamos y observaciones a solicitudes de patentes, diseños industriales, modelos de utilidad, en el ejercicio de medidas cautelares y en otras acciones o medidas similares.

A este efecto, lo(s) faculto(amos) para elevar solicitudes, formular descripciones, enmiendas, protestas, declaraciones, oposiciones, cancelaciones, nulidades, apelaciones y reclamos, pagar impuestos, cuotas y gravámenes prescritos por la ley, renunciar o desistir a derechos concedidos o en curso de concesión, recibir toda clase de documentos y valores, dando el descargo respectivo, y, en general, para dar ante dichas autoridades todos los pasos necesarios al efecto indicado y tomar todas las medidas que creyeran conducentes al resguardo de mis (nuestros) intereses, con todas las demás facultades legales necesarias.

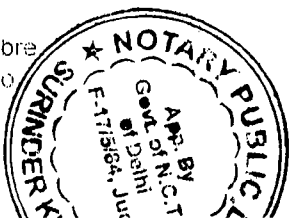
Este poder comprende la facultad de ratificar o confirmar en mi (nuestro) nombre lo actuado así como la facultad de desistir, transigir, comprometer, y la de sustituirlo en todo o en parte y revocar sustituciones. Asimismo nombro(amos) a: JUAN PABLO CADENA SARMIENTO y/o CARLOS H. PALACIO EASTMAN y/o MARTIN E. TORRES CARDOZO domiciliado(s) en la Carrera 7 No. 71-21, Torre B, Piso 4, mis (nuestros) intereses en Bogotá, Colombia, con facultades para recibir notificaciones, designar apoderados judiciales o extrajudiciales.

Otorgado y firmado en

hoy de de

Firma

Nombre  
Cargo



ATTESTED  
NOTARY PUBLIC  
DELHI

POWER OF ATTORNEY

I (We), Panacea Biotec Ltd.

domiciled in, B-1 Extn./A-27, Mohan Co-operative Industrial Estate, Mathura Road, New Delhi - 110 044 - INDIA

Hereby appoints JUAN PABLO CADENA SARMIENTO and/or CARLOS H. PALACIO EASTMAN and/or MARTIN E. TORRES CARDOZO, of Bogotá, Colombia, my (our) true and lawful attorneys with special, ample and sufficient power to obtain from the Colombian administrative, judicial and police offices and authorities, in any instance, privileges of patents of invention, registration of trademarks, industrial designs and utility models; registration of commercial names, slogans and emblems, registration of copyright and contracts related thereto; certificates of obtainers of vegetables varieties, as well as extensions, renewals and recordal of assignments and changes of name, domicile and/or address related to the above; to prepare, prosecute and register licenses of any kind; to act as plaintiff or defendant in any instance or recourse, and before any judge, corporation, public official or authority in judicial, administrative and police actions, such as: oppositions to the registration of trademarks, caducity, cancellation and nullity actions, claim actions derived from the obtaining or exploitation of licenses, action of unfair competition; criminal proceedings, actions for payment of damages; claims or observations on patent applications, models, industrial designs and utility models; in the exercise of preventive measures and in other actions or similar proceedings.

To that effect they hereby empowered to file applications, formulate descriptions, amendments, protests, declarations, oppositions, cancellations, nullities, appeals and claims; to pay taxes, quotas and assessments prescribed by law, renounce or waive the rights granted or in the process of granting; to receive all kinds of documents and valuables, giving the respective release of receipt, and, in general, to take before said authorities the necessary steps to such effect, and any measures that they may deem pertinent to the safeguard of my (our) interest(s) with all the other necessary legal powers.

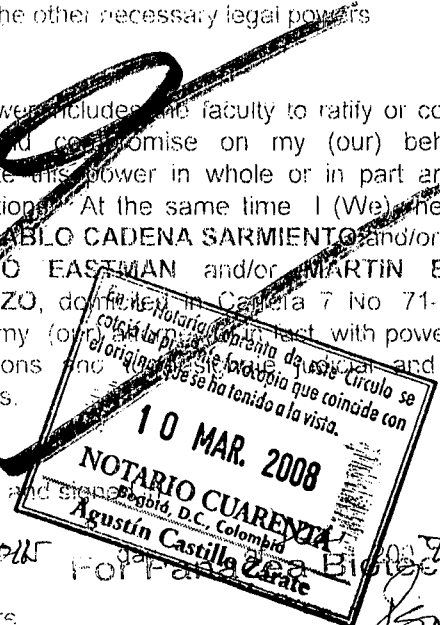
This power includes the faculty to ratify or confirm, desist, settle and compromise on my (our) behalf, and to substitute this power in whole or in part and to revoke substitutions. At the same time I (We) hereby appoint JUAN PABLO CADENA SARMIENTO and/or CARLOS H. PALACIO EASTMAN and/or MARTIN E. TORRES CARDOZO, domiciliado(s) en la Carrera 7 No. 71-21, Torre B, Piso 4, my (our) interests in Bogotá, Colombia, with powers to receive notifications and extrajudicial communications.

Granted and signed

this 20th

Signature

Name  
Title



Panacea Biotec Ltd.  
P.S. PANWAR  
Manager  
Intellectual Property & Legal Affairs

299

CERTIFICADO NOTARIAL (SOCIEDAD)

NOTARIAL CERTIFICATE (CORPORATION)

Hoy de personalmente compareció ante mí,

On this day of personally appeared before me, P. S. Panwar

a quien conozco, y de quien me consta que firmó el anterior documento, debidamente juramentado declaró y dijo que él (ella) es

to me known, and known to me to be the person who signed the foregoing instrument who being by me duly sworn did depose and say that he (she) is the Manager, INTELLECTUAL PROPERTY AND LEGAL AFFAIRS, of, Panacea Biotec Ltd. B-1 Extra, G-3, M.C.I.E., MATHURA ROAD, NEW DELHI-110044, INDIA

de, Panacea Biotec Ltd.

Which is legally constituted for a term not yet expired, that deponent is authorized by said Company to confer this Power of Attorney; that the seal affixed hereunto by the deponent in the name and on behalf of said Corporation is the corporate seal thereof; and that the purpose for which this instrument is granted is included within the corporate purpose of company.

Sociedad legalmente constituida para un periodo de duración que aún no ha terminado; que el declarante está autorizado por dicha compañía para conferir este poder; que el sello estampado por él al pie de tal poder, en nombre y representación de la expresada compañía, es el sello oficial de ella; y que el objeto para el cual se confiere este instrumento está comprendido dentro del objeto social de la sociedad.

El suscrito Notario hace constar que tuvo a la vista las pruebas de la existencia de la sociedad. The undersigned Notary Public attests that he has seen the documents that prove the existence of the company.

Estado de con fecha



State of DELHI Under date of 22.12.2007

y que quien confiere el presente poder es su representante and that he (she) who grants the present power of attorney is its Representative.



Notario Público (sello)

Public Notary (Seal)

CERTIFICADO NOTARIAL PERSONA NATURAL

NOTARIAL CERTIFICATE NATURAL PERSON

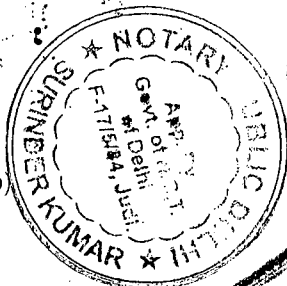
*Jasprem Singh*  
(JASPREM SINGH)  
Asstt. Secretary  
Delhi Chamber of Commerce  
New Delhi

Hoy de de , compareció(eron) ante mí

On this day of personally appeared before me

a quien (es) conozco y me consta que es(son) la(s) persona(s) firmante(s) del documento que precede y quien(es) declara(n) que otorga(n) el mismo para los fines y propósitos que en él se expresan.

who is(are) known to me and who I attest executed the foregoing document and he (they) declared he (they) grant(s) the document for the uses and purposes therein expressed.



Notario Público (sello)

**ATTESTED**  
NOTARY PUBLIC  
DELHI (INDIA)

24 DEC 2007

Notary Public (Seal)

LEGALIZACIÓN ANTE CONSUL COLOMBIANO REQUERIDA.

LEGALIZATION BEFORE THE COLOMBIAN CONSUL IS REQUIRED.



PAGADO IMPORTE DE TIENRE US\$ 10'  
PAGADO DE DERECHOS CONSULARES US\$ 15 "

**CONSULADO DE COLOMBIA**  
NUEVA DELHI

No. 65/08

El suscrito Cónsul de Colombia CERTIFICA  
que el señor G. Harshappan  
que autoriza el presente documento, ejerce  
legalmente en la fecha allí expresada las  
funciones de Ministro de Relaciones Ex.  
y que la firma y sello que en el documento  
aparecen como suyos son los que usa y  
acostumbra en sus actos oficiales.

El Cónsul no asume responsabilidad alguna  
por el contenido del documento.



*Buedo*  
**OLYMPIA LEON DE SINGH**  
Consulado de Colombia

004957  
COPIA DE LA FIRMA  
DOCUMENTO BESEMPEÑA  
LAS FUNCIONES INDICADAS

MINISTERIO DE  
RELACIONES  
EXTERIORES

2008 JAN 28 P 12:15  
EFE DE LEGALIZACIONES  
BOGOTA D.C.

NO ASUME  
RESPONSABILIDAD  
DEL TEXTO

200838 Date 31 DEC 2007

वर्तमान प्रमाण के सहायक सचिव/उप सचिव /  
उपनिवेश के सहायक सचिव/उप सचिव /  
The Signature of the Secretary /  
The Signature of the Secretary / Secretary of Chamber  
The Signature of the Secretary / Secretary of Chamber  
attested.

(जी. हर्षपान/G. HARSHAPPAN)  
अनुभाग अधिकारी (जी.आई.)  
Section Officer (G.I.)  
सी.पी.डी. शाखा/CPV Division  
विदेशी व्यापार विभाग, नई दिल्ली  
Ministry of External Affairs, New Delhi



En la Notaría Cuarenta de este Circulo se  
cotejó la presente fotocopia que coincide con  
el original que se ha tenido a la vista.  
10 MAR. 2008  
NOTARIO CUARENTA  
Bogotá, D.C., Colombia  
Agustín Castillo Zárate



No. 09-008313-00000-0000

Fecha: 2009-01-29 16:34:09

Dep. 2020 NUECREACION

Tra. 11 PATENTEIYI

Eve: 379 FASENACIONALII

Act. 411 PRESENTACION

Folios: 99

## REQUISITOS MINIMOS PARA ADMISION A TRAMITE PCT

PATENTE DE INVENCION

[X]

MODELO DE UTILIDAD

[ ]

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

COMPLETA [ ]

INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

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

COMPLETA [ ]

INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

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

COMPLETA [ ]

INCOMPLETA [ ]

Edgar Macario

Firma Responsable

Fecha

29-01-09

Carrera 13 No. 27-00 Piso 6, 7 y 10

Corrutador: 3 82 08 40

Fax: 350 52 20

E-mail: [info@sic.gov.co](mailto:info@sic.gov.co)

[www.sic.gov.co](http://www.sic.gov.co)

Bogotá, D.C., Colombia

**REPUBLICA DE COLOMBIA**  
**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO**

Bogotá,  
2020

Doctor(a)  
CADENA SARMIENTO JUAN PABLO  
Apoderado(a) y/o Representante de  
PANACEA BIOTEC LIMITED

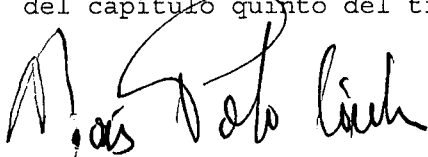
|            |                            |                  |
|------------|----------------------------|------------------|
| REFERENCIA | Radicación No.             | 9 8313           |
|            | Solicitud internacional    | PCT/IN2007/00274 |
|            | Fecha inicio fase nacional | 07/02/2009       |
|            | Trámite                    | 11               |
|            | Evento                     | 379              |
|            | Actuación                  | 430              |
|            | Oficio No.                 | 2255             |

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. Si fuere el caso, el solicitante debe adjuntar la traducción de los anexos del reporte de examen preliminar internacional (Art. 36.2.b) del tratado PCT.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No.10 de 2001.



DORIS ELENA POLO CORDOBA  
Jefe de la división de Nuevas Creaciones (E)

El anterior requerimiento fue notificado por fijación en lista de  
fecha 27 FEB. 2009  
adpa11