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Eve: 1 REGDEPOSITO

Act 444 RESPUESTAREQUE

Folios: 11

Respuesta a Oficio No. 5569 del 25 de mayo de 2006

REF: Expediente No. 01 001 317 - solicitud de patente de invención
a favor de ASTRAZENECA AB.

JUAN PABLO CADENA SARMIENTO, portador de la tarjeta profesional No. 57.492 del C.S.J., obrando como apoderado sustituto de la sociedad ASTRAZENECA AB, domiciliada en Sodertälje, Suecia, según lo acredita el documento de poder anexo, me permito dar respuesta a las observaciones de carácter técnico y jurídico, relacionadas con la patentabilidad, para la concesión de la patente de acuerdo con la Decisión 486 según el concepto técnico No. 787 notificado por fijación en lista de fecha 25 de mayo de 2006.

Atendiendo las observaciones del señor Examinador, en relación con el artículo 46 de la Decisión 486 de la Comisión de la Comunidad Andina, me permito anexar al presente escrito el siguiente documento:

• JOHN C. WATERTON ET AL.: "A case of adenomyosis in a pigtailed monkey diagnosed by magnetic resonance imaging and treated with the novel pure antiestrogen, ICI 162,780" LABORATORY ANIMAL SCIENCE, vol. 43, No. 3, 1993, pages 247-251 XP000998289.

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Expediente No. 01 001 317

Con lo anterior hemos dado total cumplimiento a los requerimientos del señor examinador, consideramos por lo tanto que la solicitud se encuentra en condiciones de ser permitida.

De la Señora Jefe,

Atentamente,



JUAN PABLO CADENA SARMIENTO

T.P. No. 57.492 del C.SJ.

C.C. 80.410.337 de Usaquén

Carrera 7 No. 16-56 piso 9

Bogotá, 22 de agosto de 2006

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Anexos

A Case of Adenomyosis in a Pigtailed Monkey Diagnosed by Magnetic Resonance Imaging and Treated with the Novel Pure Antiestrogen, ICI 182,780

John C. Waterton¹, Seán A. Breen¹, Michael Duker², Maureen Horrocks², and Peter F. Wadsworth²

The menstrual cycle occurs in Old World monkeys, apes, and humans. The pathologic occurrence of heterotopic uterine endometrial tissue is common in these species, particularly in captive nonhuman primates (1) and in humans. Adenomyosis is the occurrence of endometrium within the myometrium, while endometriosis is the occurrence of endometrium outside the uterus, for example, on the serosal surface of the myometrium or bowel, on the ovaries, or within the pelvic adipose tissue. The disorder in primates provides an excellent model of the human disease. Human endometriosis is commonly treated with endocrine agents such as danazol or goserelin, and adenomyosis can be expected to respond similarly. In macaques, also, endometriosis can be successfully treated with hormone analogue therapy (2). Early disease is, however, often asymptomatic, and early diagnosis is difficult, although now possible with magnetic resonance imaging (MRI) (3-6). Magnetic resonance imaging noninvasively yields quantitative, three-dimensional information about the soft tissues; it has consequently proved useful to quantitatively assess the response of benign uterine lesions to therapy (9-12). Herein we describe a case of adenomyosis in a pigtailed monkey (*Macaca nemestrina nemestrina*) diagnosed by MRI and treated with the pure estrogen antagonist, ICI 182,780.

This case was encountered in the course of a series of studies in monkeys of the efficacy and pharmacology of novel endocrine agents being developed to treat hormone-dependent cancers (13, 14). Magnetic resonance imaging was performed on 23 untreated asymptomatic mature females, using the multilayer oblique MRI techniques described previously (16). The case we describe was in the only 1 of 23 monkeys discovered to have any obvious abnormality by MRI. The uterus occupied 25.3 cm³ and was substantially enlarged, grossly distorted, and asymmetric (Figure 1), with patchy high-signal features in the myometrium.

This monkey was a mature (8.4 kg) female. It was sexually mature when imported from Indonesia directly to these laboratories. After 6 months' quarantine, it was housed thereafter with another female, in sight of other female and male

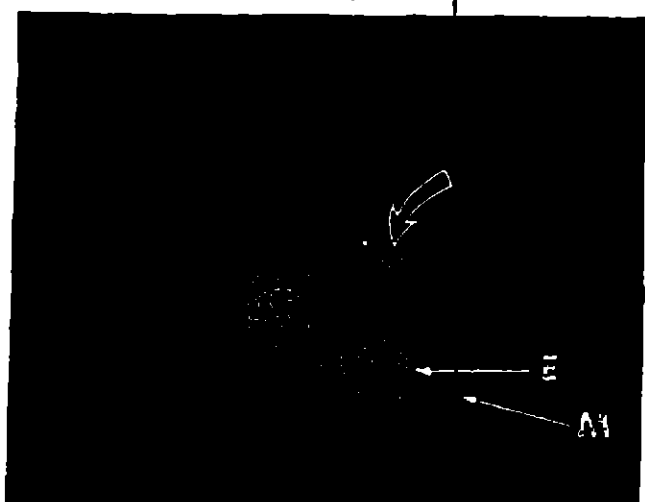
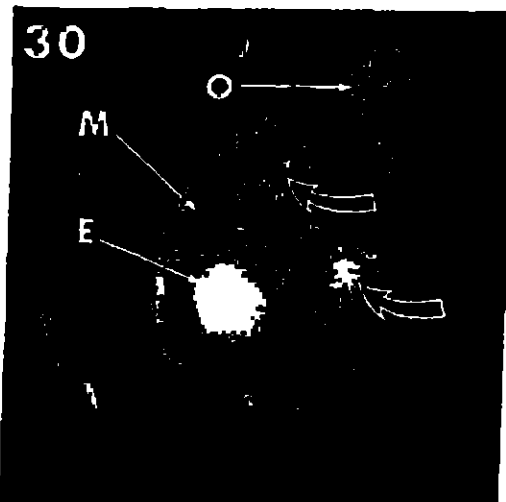
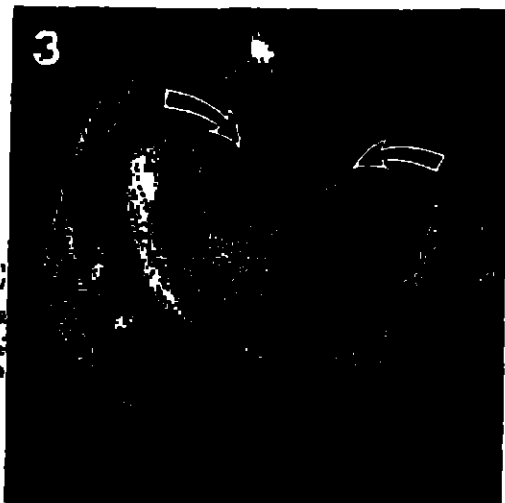
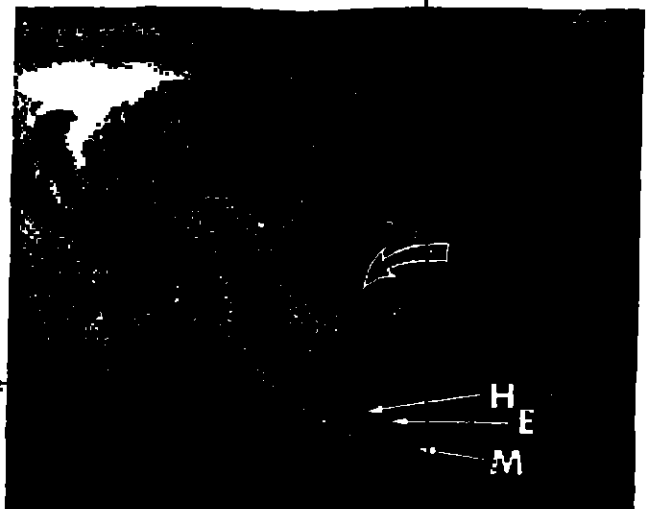
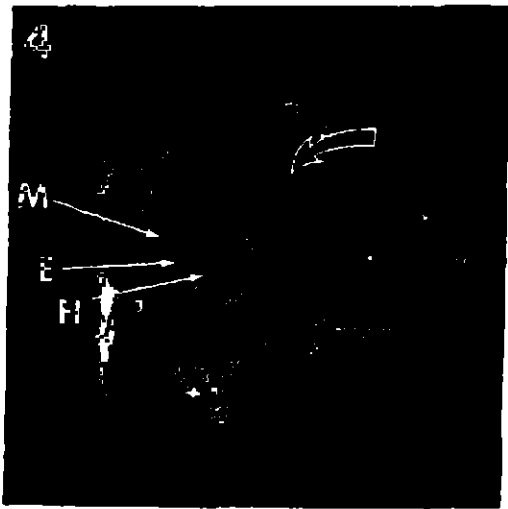
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pigtailed monkeys, at a minimum temperature of 24°C, in natural light supplemented with artificial light (7:00 a.m. to 4:00 p.m.) and fed a proprietary chow (Old World Monkey Diet, BP Nutrition Ltd., Northwich, Cheshire, U.K.) supplemented daily with fresh fruit and vegetables. It had regular menstrual cycles (detected by vaginal swabbing) during 5 years (mean length, 28 days, S.D. 4 days, n = 66), typical of the species. Hormone (estradiol and progesterone) profiles during complete menstrual cycles were determined at intervals, for which daily blood samples (2 ml) were drawn from the saphenous vein; these were also typical of the species (18). Neither swabbing nor venipuncture required removing the monkey from its cage. No uterine abnormality was noted during MRI performed 2.5 years earlier, when the uterine volume was 8.9 cm³. The animal appeared to be well throughout, and no outward signs of the developing uterine abnormality were detected.

A provisional diagnosis of adenomyosis was made. Notwithstanding the putative lesions, the animal was considered suitable for entry into an experimental protocol (12) designed to evaluate the efficacy in monkeys of a novel pure estrogen antagonist, ICI 182,780 (7 α -(4,4,5,5,5-pentafluoro-pentylsulphonyl)oxy)estra-1,3,5(10)-triene-3,17 β -diol, recently described by us (17). ICI 182,780 has high affinity for the estradiol receptor but, unlike nonsteroidal antiestrogens such as tamoxifen, has been shown to be devoid of partial agonist (estrogenic) activity. It may, therefore, offer some advantages in the treatment of breast cancer and uterine disorders such as endometriosis and adenomyosis. Six additional examinations were made during two nonconsecutive menstrual cycles. After the end of the second cycle, the monkey was treated with ICI 182,780. Two separate doses each of 4 mg/kg were given i.m. in a ester-oil-based depot formulation, on days 2 and 31 (day 1 defined as the day of onset of menstruation). This dose and formulation have previously been found to inhibit the effects of endogenous estrogen in normal animals for 3 to 4 weeks (18). Magnetic resonance imaging continued for 12 weeks, during and after treatment; in total, 17 MRI examinations were made.

The design of our method for uterine MRI and its prediction are described in detail elsewhere (14, 15). Anaesthesia for restraint during MRI was induced with ketamine (0.7

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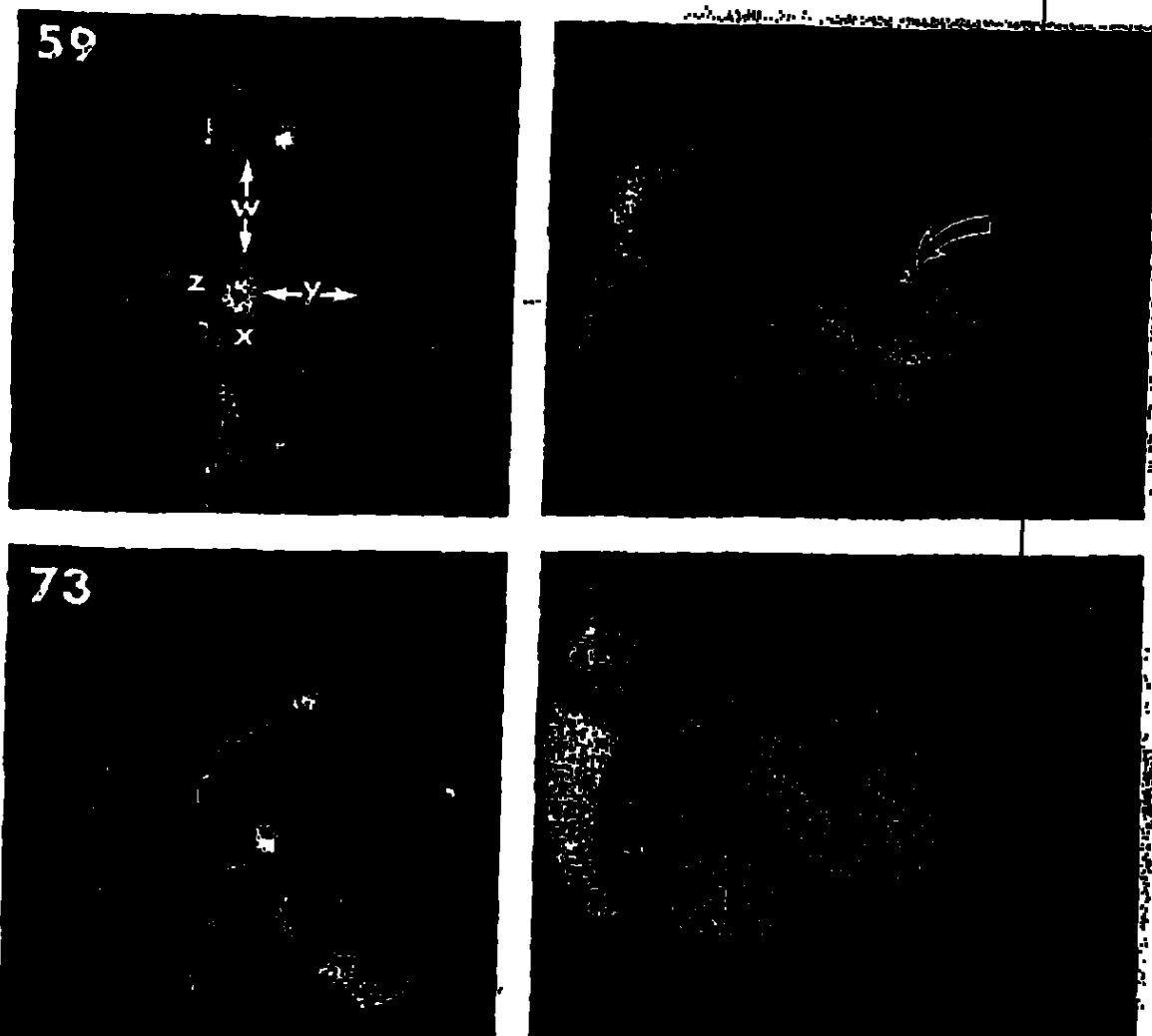


Figure 1. Magnetic resonance images before, during, and after therapy of adenomyosis in a pigtailed monkey. Each pair of images shows one of the eight oblique slices (left) and one of the eight sagittal slices (right). The sagittal images show a detail corresponding to 65 mm x 51 mm; top of the image is dorsal and left is caudal. High signal is also sometimes seen from the intervertebral discs (dorsal and cranial) and from the urinary bladder (caudal). The oblique images are transverse axial through corpus uteri and show a detail corresponding to 65 mm x 65 mm; left is ventral and caudal. Top pair (page 346), at diagnosis; second pair, at beginning of second untreated cycle; third pair, 28 days of first treatment; fourth pair (top), 28 days of second treatment showing lesion width measurement; bottom pair, 42 days after second treatment. The numbers in the figure refer to days after onset of menstruation. M, myometrium; E, endometrium; H, menstrual hematoma; O, ovary; open arrows, adenomyosis. The reported lesion width is the mean (for the two oblique midcorpal slices) of dimensions (w minus x) and (y minus z).

mg/kg i.m., Vetalar®, Parke-Davis, Eastleigh, Hampshire, U.K.) and maintained with halothane (Fluothane®, ICI Pharmaceuticals, Macclesfield, Cheshire, U.K.). We used a Biospec 400/2.3 instrument (Oxford Research Systems, Coventry, U.K.) incorporating a magnet with flux density 2.35 Tesla. The orientation of the uterus within the pelvis varies from day to day depending on the volume and disposition of the contents of the urinary bladder and distal portion of the intestines. Hence, it is advantageous for quantitative studies to use oblique MRI techniques that force

the presentation of the uterus for image analysis to be similar from examination to examination. Sagittal sighting images were used to determine the spatial coordinates of the uterine cervix and fundus. From these coordinates, MRI parameters were calculated to allow the acquisition of eight contiguous oblique slice images whose thickness, position, and orientation were forced to depend on the vector connecting the fundus and cervix. Fat-suppressed spin-echo images were acquired with an echo time of 50 msec and repetition time of 3 seconds. Image resolution in plane was

0.6 mm. This method has previously been shown to provide reproducible presentation of the uterus, independent of its size, location, and orientation in the pelvis (14). From each examination, three parameters were measured: endometrial volume (EV) obtained as described previously (14, 15) from area measurements of eight contiguous oblique slices; myometrial volume (MV) obtained similarly; and a measure of that part of the myometrial width attributable to the lesion (Figure 1).

During each untreated cycle, MV remained fairly constant; EV was high during menstruation. Ovulation occurred during both cycles, and EV increased rapidly during the subsequent luteal phase. The changes in EV were larger and more variable than observed previously in the population of healthy animals (14). The width of the lesion increased steadily during each cycle (Figure 2).

After the first dose of ICI 162,780, a similar pattern to the untreated cycles was noted, with EV and lesion width increasing in the luteal phase. However, in the 4 weeks after the second dose, EV, MV, and lesion width decreased by 87%, 67%, and 45%, respectively (Figures 1 and 2), and the lesion became much less conspicuous in MRI (Figure 1). Subsequently, some regrowth in measured lesion width was noted, but EV and MV declined further. Serum hormone measurements revealed that ovulation occurred slightly later and after higher pre-ovulatory peak estradiol concentrations than in earlier untreated cycles (1460 pmol/l on day 22, compared with 500 to 540 pmol/l on days 17 to 20) and was followed by a normal luteal phase pattern of progesterone secretion (3.2 to 22.1 nmol/l) lasting 14 days. During 29 days after the second treatment, plasma estradiol concentrations fluctuated between 40 and 257 pmol/l, except for a peak of 1,117 pmol/l on cycle day 21; progesterone concentrations remained at basal values (0.32 to 1.93 nmol/l) throughout this period. Ovulation therefore did not occur.

Eighty days after treatment began, the monkey was euthanized by intravenous injection of sodium pentobarbitone (Ruthala[®], May and Baker, Dagenham, Essex, U.K.) before it recovered consciousness after completing the last MRI procedure. No gross abnormalities were observed at necropsy. Histologic examination of the uterus disclosed multifocal endometrial tissue scattered throughout the myometrium (adenomyosis). In addition, small foci of endometriosis were present within adipose tissue adjacent to the ovaries and uterus.

A second retrospective examination of the magnetic resonance images revealed occasional small high-signal foci within the adipose tissue and on the serosal surface of the uterus, consistent with the endometriosis noted during histologic examination. However, under our MRI conditions, these were nonspecific and too small to be diagnostically useful or quantifiable. Although adenomyosis is not routinely treated in women (except perhaps incidentally during therapy for endometriosis or leiomyoma), the lesions are quite analogous to endometriosis and, hence, could be expected to respond to the same hormonal therapies (18). We conclude that asymptomatic adenomyosis in monkeys can be diagnosed by MRI; and that removing the endogenous estrogen drive by means

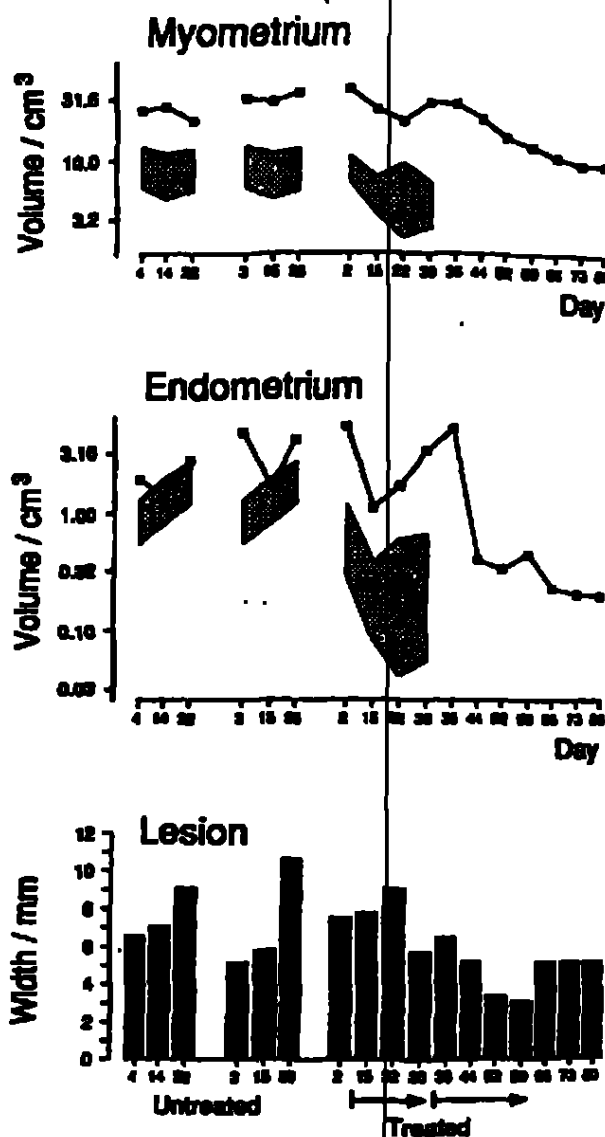


Figure 2. Response of myometrial volume, endometrial volume, and lesion width during two untreated cycles and two consecutive antiestrogen treatments. The stippled areas represent values for normal animals (mean $\pm$ 1 SD), untreated ($n = 10$) or treated with a single depot of ICI 162,780 (4 mg/kg, i.m., $n = 6$). Each volume was measured independently by two observers (J. C. W., B. A. B.) and the mean is shown. Each lesion width value is the mean for the same four locations in the uterus; two of which are shown in Figure 1. Days are referred to the day of onset of the most recent menstruation.

of pure estrogen antagonist was, in this case, beneficial in reducing the size of the lesion.

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BOGOTA - COLOMBIA

PODER

Yo (nosotros)

domiciliado(s) en

Nombro(amos) a: RAMIRO CASTRO DUQUE y/o JUAN PABLO CADENA SARMIENTO y/o BEATRIZ JARAMILLO S.

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 y enseñanzas, 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 y/o domicilio; 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 desistirse 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 desistirse, transigir, comprometer, y la de sustituirlo en todo o en parte y revocar sustituciones. Asimismo nombro(amos) a: RAMIRO CASTRO DUQUE y/o JUAN PABLO CADENA SARMIENTO y/o BEATRIZ JARAMILLO S. domiciliado(s) en la Carrera 7 No. 18-58 Piso 9, mis (nuestros) apoderados en Colombia, con facultades para recibir notificaciones y designar apoderados judiciales o extrajudiciales.

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Firma

Nombre
Cargo

POWER OF ATTORNEY

I (We) ASTRAZENECA AB

domiciled in SE-151-50derta1je, Sweden

Hereby appoint RAMIRO CASTRO DUQUE and/or JUAN PABLO CADENA SARMIENTO and/or BEATRIZ JARAMILLO S.

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 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 and domicile 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; penal demands, actions of indemnities for 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 are 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 kind 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.

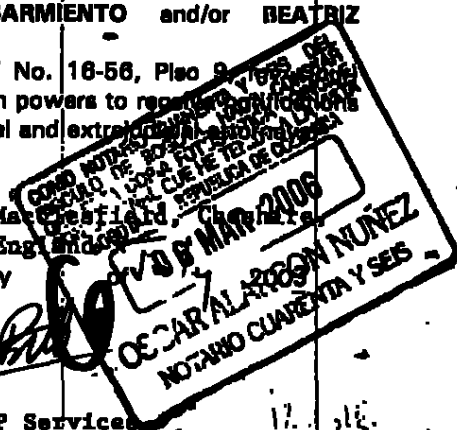
This power includes the faculty to ratify or confirm deal, settle and compromise on my (our) behalf, and to substitute this power in whole or in part and to revoke substitutions. At the same time I (We) hereby appoint RAMIRO CASTRO DUQUE and/or JUAN PABLO CADENA SARMIENTO and/or BEATRIZ JARAMILLO S.

domiciled in Carrera 7 No. 18-58, Piso 9, my (our) attorney(s) in fact, with powers to receive notifications and to designate judicial and extrajudicial attorneys.

Granted and signed in Macao, China, this 18th day of March 2006

Signature

Name KEVIN BILL
Title Director, IP Services



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a quien conozco, y de quien me consta que firmó el
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Estado de
con fecha

y que quien confiere el presente poder es su
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On this 18th day of July 2003 of
personally appeared before me
KEVIN BILL

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

ATTORNEY

of

ATRAZENECA AB

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
Corporation is the corporate seal thereof; and that
purpose for which this instrument is granted
included within the corporate purpose of company.

The undersigned Notary Public attests that he has seen
the documents that prove the existence of the
company.

State of Sweden
under date of 1st January 2003

and that he (she) who grants the present power of
attorney is its Representative.

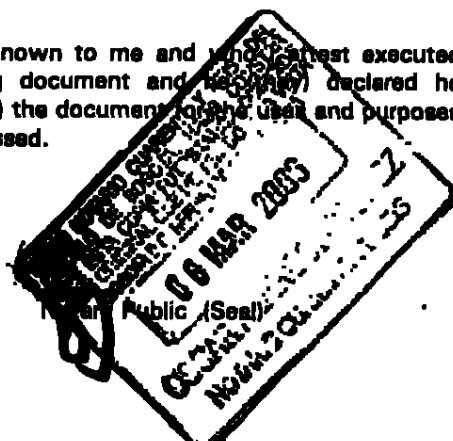
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On this day of of
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who is(are) known to me and who has(they) executed
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6. the/le 17 February 2004

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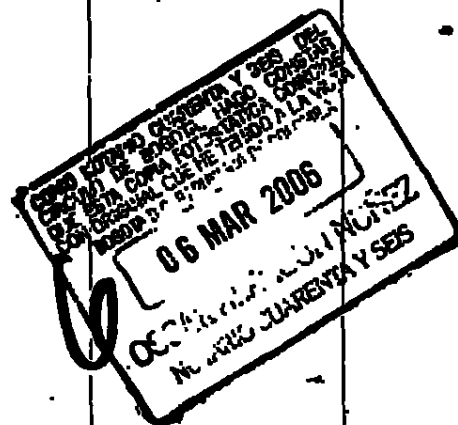
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(Convención de La Haya del 5 de Octubre de 1961)

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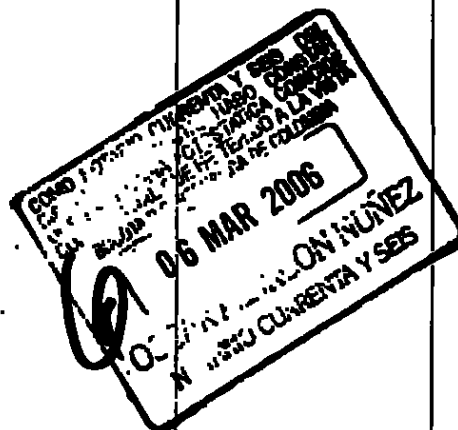
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5. en Londres
6. el 17 de Febrero de 2004
7. por El secretario de Estado Principal de Su Majestad, para Asuntos Exteriores y de la Comunidad
8. No. **G348987**
9. Sello
10. Firma

J. Ireland (Firma)

Si este documento va a ser utilizado en un país que no es parte de la Convención de La Haya del 5 de Octubre de 1961, debe ser presentado a la sección consular de la misión, que representa a ese país.





ORGANIZACIÓN ELECTORAL
REGISTRADURÍA NACIONAL DEL ESTADO CIVIL

GAVIRI A

REGISTRO CIVIL DE DEFUNCIÓN

Indicativo
Serial

5562241

Datos de la oficina de registro											
Clase de oficina:	Registraduría	Notaría	☒	Consulado		Corregimiento		Insp. de Policía		Código	9795
País: Colombia - Municipio: Cundinamarca - Corregimiento: de Inspección de Policía											
COLOMBIA CUNDINAMARCA BOGOTA D.C.										NOTARIA 32.	

Datos del inscrito	
Apellidos y nombres completos	
CASTRO DUQUE RAMIRO	
Documento de identificación (Clase y número)	Sexo (en Letras)
C.C. No. 170322 DE BOGOTA	MASCULINO

Datos de la defunción	
Lugar de la Defunción: País - Departamento - Municipio - Corregimiento de Inspección de Policía	
COLOMBIA CUNDINAMARCA BOGOTA D.C.	
Fecha de la defunción	Hora
Año 2004 Mes 10 Día 30 04:10 PM	Número de certificado de defunción
A- 2094375.	
Presunción de muerte	
Jurado que profiere la sentencia	Fecha de la sentencia
Documento presentado	
Autorización Judicial	Certificado Médico
☐	☒
Nombre y cargo del declarante	
ANDRES DIAZ CAMPOS.-	
R.M. No. 79982662	

Datos del denunciante	
Apellidos y nombres completos	
EDGAR DAVID REGINO II.	
Documento de identificación (Clase y número)	Firma
C.C. No. 15.030.154 DE LORICA/ CORDOBA	

Primer testigo	
Apellidos y nombres completos	
Documento de identificación (Clase y número)	
Firma	

Segundo testigo	
Apellidos y nombres completos	
Documento de identificación (Clase y número)	
Firma	

Fecha de inscripción	
Año 2004 Mes 11 Día 02	Notario y firma del notario que declara
BLANCA NOTARIO RESTREPO	

PADRES: ALFONSO CASTRO	
MERCEDES DUQUE.	

ORIGINAL PARA LA OFICINA DE REGISTRO

NOTARIA 32

DEL CIRCULO DE SANTA FE DE BOGOTA, D.C.

Germán Eleázar Moreno L.
Notario

COMO SECRETARIO DELEGADO DE LA NOTARIA TREINTA Y DOS (32) DEL
CIRCULO DE BOGOTA

CERTIFICO, QUE:

La presente acta es fiel copia del original tomada del registro
civil de defunciones serial indicativo número: **576224**
que expido en la ciudad de Bogotá D.C. hoy: **05 NOV. 2004**

NOTARIA 32 DEL CIRCULO DE BOGOTA D.C.
SECRETARIO DELEGADO

HELEON FLORES G.
SECRETARIO DEL PRADO PARA COPIAS
ORDEN 1334 DE 1999



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All: 1 Review: 0

☐ 1: Br J Cancer. 1996 Jul;74(2):300-8.

Links

Pharmacokinetics, pharmacological and anti-tumour effects of the specific anti-oestrogen ICI 182780 in women with advanced breast cancer.

Howell A, DeFriend DJ, Robertson JF, Blamey RW, Anderson L, Anderson E, Sutcliffe FA, Walton P.

CRC Department of Medical Oncology, University of Manchester, Christie Hospital, UK.

We have assessed the pharmacokinetics, pharmacological and anti-tumour effects of the specific steroidal anti-oestrogen ICI 182780 in 19 patients with advanced breast cancer resistant to tamoxifen. The agent was administered as a monthly depot intramuscular injection. Peak levels of ICI 182780 occurred a median of 8-9 days after dosing and then declined but were above the projected therapeutic threshold at day 28. C_{max} during the first month was 10.5 ng/ml-1 and during the sixth month was 12.6 ng ml-1. The AUCs were 140.5 and 206.8 ng day ml-1 on the first and sixth month of dosing respectively, suggesting some drug accumulation. Luteinising hormone (LH) and follicle-stimulating hormone (FSH) levels rose after withdrawal of tamoxifen and then plateaued, suggesting no effect of ICI 182780 on the pituitary-hypothalamic axis. There were no significant changes in serum levels of prolactin, sex hormone-binding globulin (SHBG) or lipids. Side-effects were infrequent. Hot-flushes and sweats were not induced and there was no apparent effect of treatment upon the endometrium or vagina. Thirteen (69%) patients responded (seven had partial responses and six showed 'no change' responses) to ICI 182780, after progression on tamoxifen, for a median duration of 25 months. Thus ICI 182780, given by monthly depot injection, and at the drug levels described, is an active second-line anti-oestrogen without apparent negative effects on the liver, brain or genital tract and warrants further evaluation in patients with advanced breast cancer.

PMID: 8688341 [PubMed - Indexed for MEDLINE]

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Related Links

Response to a specific antioestrogen (ICI 182780) in tamoxifen-resistant breast cancer. [Lancet. 1995]

Phase II study of vorozole (R83842), a new aromatase inhibitor, in postmenopausal women with advanced breast cancer in progression on tamoxifen. [Cancer Res. 1995]

Investigation of a new pure antiestrogen (ICI 182780) in women with primary breast cancer. [Cancer Res. 1994]

Phase I study of the tolerance and pharmacokinetics of toremifene in patients with breast cancer. [Cancer Res Treat. 1990]

ICI 182,780 (Faslodex): development of a novel, "pure" antiestrogen. [Cancer. 2000]

See all Related Articles...

121
127
D3

③

EUROPEAN PATENT APPLICATION

⑦ Application number: 89308563.2

⑫ Int. Cl.: A61K 31/565 , //(A61K31/565,
31:165)

⑧ Date of filing: 02.06.89

④ Claims for the following Contracting States: ES + GR. ⑨ Priority: 06.06.88 GB 8813353 ⑩ Date of publication of application: 13.12.89 Bulletin 89/50 ⑬ Designated Contracting States: AT BE CH DE ES FR GB GR IT LI LU NL SE	⑭ Applicant: IMPERIAL CHEMICAL INDUSTRIES PLC Imperial Chemical House Millbank London SW1P 3JF(GB) ⑮ Inventor: Dulake, Michael 84 Stylai Road Wimslow Cheshire, SK9 4AQ(GB) ⑯ Representative: Slatcher, Reginald Peter et al Imperial Chemical Industries PLC Legal Department Patents PO Box 8 Welwyn Garden City Herts, AL7 1HD(GB)
---	--

⑰ Therapeutic product.

⑱ The invention relates to a therapeutic product comprising an oestrogen and a pure antioestrogen for simultaneous, sequential or separate use in selective oestrogen therapy of perimenopausal or postmenopausal conditions; to a process for the manufacture of said product and to a pharmaceutical composition containing said product. The invention also relates to a pharmaceutical composition comprising an oestrogen and a pure antioestrogen and to a process for the manufacture of said composition.

EP 0 346 014 A1

12/12/01

TABLE III

Treatment	Uterine Weight (mg)	Calculated Inhibition
Untreated Controls	302 ± 38	
Ovariectomised Controls	70 ± 1.3	
Test Compound (mg/kg)		
0.1	208 ± 17	41
0.3	174 ± 18	55
1	94 ± 8	90
3	103 ± 2	88

TABLE IV

Treatment	Gross Femur Density (g/ml)	Calculated Inhibition
Untreated Controls	1.523 ± 0.008	
Ovariectomised Controls	1.481 ± 0.008	
Test Compound at (mg/kg)		
0.1	1.528 ± 0.006	0%
0.3	1.528 ± 0.008	0%
1	1.532 ± 0.006	0%
3	1.533 ± 0.006	0%

Example 3

The pure antioestrogen used was 7- α -[8-(4,4,5,5,5-pentafluoropentylsulphonyl)nonyl]oestra-1,3,5(10)-triene-3,17 β -diol.

Each of a series of selected doses of this compound was dissolved in a mixture of castor oil and benzyl alcohol and given by intramuscular injection to a group of 5 mature rats. The formulation contained 50 mg of the test compound, 400 mg of benzyl alcohol and sufficient castor oil to bring the solution to a volume of 1 ml. In each case a second dose was administered two weeks after the first dose. Two weeks after the second dose the weights of the uteri of the test groups of rats were determined. In addition the femurs were dissected and analysed for Gross Femur Density as in Example 1.

A further group of rats, given two injections of castor oil separated by a two week period, served as an intact control group. A further group of rats was ovariectomised to serve as another control group.

The results shown below in Tables V and VI demonstrate that at all doses tested the compound selectively inhibits the action of the animals' endogenous oestrogen on their uteri whereas at the two higher test doses there was no significant inhibition of gross femur density.

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification: A61K 31/565, 9/08, 47/44	A1	(11) International Publication Number: WO 97/21440 (43) International Publication Date: 19 June 1997 (19.06.97)
(21) International Application Number: PCT/GB96/03022 (22) International Filing Date: 9 December 1996 (09.12.96) (30) Priority Data: 9525194.8 12 December 1995 (12.12.95) GB (71) Applicant (for all designated States except US): ZENBCA LIMITED (GB/GB); 15 Stanhope Gate, London W1Y 6LN (GB). (72) Inventors; and (73) Inventors/Applicants (for US only): FERDINANDO, Josephine, Joan, Christine (GB/GB); Frankland Road, Blagrove, Swindon, Wiltshire SN5 8YS (GB). HUTCHINSON, Keith, Graeme (GB/GB); Frankland Road, Blagrove, Swindon, Wiltshire SN5 8YS (GB). PARKER, Roy (GB/GB); Frankland Road, Blagrove, Swindon, Wiltshire SN5 8YS (GB). (74) Agent: TAFT, Brian, Steele; Zeneca Pharmaceuticals, Intellectual Property Dept., Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG (GB).	(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published With international search report.	
(54) Title: A SOLUTION FOR ORAL ADMINISTRATION CONTAINING ICI 182,780 (57) Abstract The invention concerns a pharmaceutical composition in the form of a solution formulation adapted for oral administration which comprises ICI 182,780, a pharmaceutically-acceptable oil, a pharmaceutically-acceptable lipophilic surfactant, a pharmaceutically-acceptable hydrophilic surfactant, and a pharmaceutically-acceptable water-miscible solvent, and the use of the composition on oral administration to a warm-blooded animal to produce an antioestrogenic effect.		

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- 15 -

CLAIMS

1. A pharmaceutical composition in the form of a solution formulation adapted for oral administration which comprises:-
- 5 (i) ICI 182,780;
- (ii) a pharmaceutically-acceptable oil;
- (iii) a pharmaceutically-acceptable lipophilic surfactant;
- (iv) a pharmaceutically-acceptable hydrophilic surfactant; and
- (v) a pharmaceutically-acceptable water-miscible solvent.
- 10
2. A pharmaceutical composition as claimed in claim 1 wherein the pharmaceutically-acceptable oil is a triglyceride of a C6 to C12 fatty acid or a diglyceride of a C14 to C20 fatty acid.
- 15 3. A pharmaceutical composition as claimed in claim 1 wherein the pharmaceutically-acceptable oil is fractionated coconut oil.
4. A pharmaceutical composition as claimed in claim 1 wherein the pharmaceutically-acceptable lipophilic surfactant is a mixture of mono- and di-glycerides
- 20 of capric and caprylic acids.
5. A pharmaceutical composition as claimed in claim 1 wherein the pharmaceutically-acceptable hydrophilic surfactant is the condensation product of ethylene oxide with castor oil or with hydrogenated castor oil.
- 25
6. A pharmaceutical composition as claimed in claim 1 wherein the pharmaceutically-acceptable water-miscible solvent is ethanol, propylene glycol, diethylene glycol mono-ethyl ether or diethylene glycol mono-tetrahydrofurfurylmethyl ether, or a mixture thereof.
- 30

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7. A pharmaceutical composition as claimed in claim 1 wherein the relative ratios of the ingredients (as percentages of the weight of the formulation) are:-

ICI 182,780	2-18%
oil	2-18%
hydrophilic surfactant	10-40%
lipophilic surfactant	25-60%
water-miscible solvent	2-28%

5 8. A pharmaceutical composition as claimed in claim 1 wherein the relative ratios of the ingredients (as percentages of the weight of the formulation) are:-

ICI 182,780	5-15%
oil	5-15%
hydrophilic surfactant	20-30%
lipophilic surfactant	35-50%
water-miscible solvent	5-25%

9. A pharmaceutical composition as claimed in claim 1 wherein the relative
10 ratios of the ingredients (as percentages of the weight of the formulation) are:-

ICI 182,780	8-12%
oil	5-15%
hydrophilic surfactant	20-30%
lipophilic surfactant	35-50%
water-miscible solvent	8-16%

10. The use of a pharmaceutical composition as claimed in any one of claims 1 to
9 in the manufacture of a medicament for oral administration to a warm-blooded animal to
15 produce an antioestrogenic effect.

Comparative Example 1

The solution formulation comprised the ingredients shown below. Addition of the formulation to aqueous sodium chloride resulted in the formation of a precipitate which was noted to aggregate over a period of about 10 minutes.

5

Ingredient	% weight	Pharmacokinetic Parameter	
	(g per 100 ml)		
ICI 182,780	2.0	Dose	50 mg
ethanol	10.0	Cp (max)	13.3 ± 2.7 ng ml ⁻¹
water	8.0	AUC (0 to 8 hours)	34.9 ± 6.3 ng h ml ⁻¹
propylene glycol	to 100%	Bioavailability	1.1 %

Comparative Example 2

The solution formulation comprised the ingredients shown below. Addition of the formulation to aqueous sodium chloride resulted in the formation of a crude emulsion.

10

Ingredient	% weight	Pharmacokinetic Parameter	
	(g per 100 ml)		
ICI 182,780	10.0	Dose	50 mg
ethanol	13.5	Cp (max)	14 ± 2 ng ml ⁻¹
Imwitor 988	76.5	AUC (0 to 8 hours)	28 ± 5 ng h ml ⁻¹
		Bioavailability	0.8 %

Comparative Example 3

The solution formulation comprised the ingredients shown below. Addition of the formulation to aqueous sodium chloride resulted in the formation of a hazy, opalescent

15 mixture, the turbidity of which increased gradually.

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- 12 -

Ingredient	% weight	Pharmacokinetic Parameter	
	(g per 100 ml)		
ICI 182,780	10.0	Dose	50 mg
propylene glycol	10.0	Cp (max)	20 ± 4 ng ml ⁻¹
Imwitor 988	80.0	AUC (0 to 8 hours)	51 ± 10 ng h ml ⁻¹
		Bioavailability	1.5 %

Example 1

The solution formulation comprised the ingredients shown below. Addition of the formulation to aqueous sodium chloride resulted in the formation of a hazy, opalescent mixture, the turbidity of which increased gradually over a period of 8 hours. The formulation gave the pharmacokinetic parameters shown below when dosed orally to dogs.

Ingredient	% weight	Pharmacokinetic Parameter	
	(g per 100 ml)		
ICI 182,780	10.0	Dose	50 mg
Imwitor 988	40.0		
Cremophor RH40	26.8	Cp (max)	83 ± 19 ng ml ⁻¹
Miglyol 812	13.2	AUC (0 to 8 hours)	194 ± 34 ng h ml ⁻¹
ethanol	10.0	Bioavailability	5.5 %

Example 2

The solution formulation comprised the ingredients shown below. Addition of the formulation to aqueous sodium chloride resulted in the formation of a hazy, opalescent mixture, the turbidity of which increased gradually over a period of 8 hours. The formulation gave the pharmacokinetic parameters shown below when dosed orally to dogs.

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Ingredient	% weight	Pharmacokinetic Parameter	
	(g per 100 ml)		
ICI 182,780	10.0	Dose	50 mg
Imwitor 988	45.9		
Cremophor RH40	22.95	Cp (max)	78 ± 17 ng ml ⁻¹
Miglyol 812	7.65	AUC (0 to 8 hours)	193 ± 35 ng h ml ⁻¹
propylene glycol	13.5	Bioavailability	5.4 %

Example 3

The solution formulation comprised the ingredients shown below. Addition of the formulation to aqueous sodium chloride resulted in the formation of a hazy, opalescent mixture, the turbidity of which increased gradually over a period of 8 hours. The formulation gave the pharmacokinetic parameters shown below when dosed orally to dogs.

Ingredient	% weight	Pharmacokinetic Parameter	
	(g per 100 ml)		
ICI 182,780	10.0	Dose	50 mg
Imwitor 742	40.0		
Cremophor RH40	26.8	Cp (max)	80 ± 14 ng ml ⁻¹
Miglyol 812	13.2	AUC (0 to 8 hours)	195 ± 26 ng h ml ⁻¹
ethanol	10.0	Bioavailability	5.6 %

Example 4

The solution formulation comprised the ingredients shown below. Addition of the formulation to aqueous sodium chloride resulted in the formation of a hazy, opalescent mixture, the turbidity of which increased gradually over a period of 8 hours. The formulation gave the pharmacokinetic parameters shown below when dosed orally to dogs.

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020/
Bogotá, D.C.,

Doctor
Juan Pablo Cadena Sarmiento
Apoderado
ASTRAZENECA AB.

Oficio N° 10440

REFERENCIA	Radicación	01 1317
	Trámite	002
	Evento	001
	Actuación	430
	Folios	006

Como resultado del examen de patentabilidad de la solicitud de patente de invención N° 01 1317, realizado según el artículo 45 de la decisión 486 de la comisión de la Comunidad Andina, se notifica:

1. DOCUMENTOS ESTUDIADOS:

- El resumen y el capítulo descriptivo de la solicitud de los folios 29 y 5 a 21 respectivamente.
- Los ejemplos que ilustran la invención en los folios 22 y 23.
- Las cláusulas 1 a 19 relacionadas en el capítulo reivindicatorio de la solicitud y que se encuentran en los folios 25 a 28.
- Los diagramas de concentración plasmática vs tiempo en el folio 30.
- El primer examen de forma de la solicitud de oficio No. 1034 que se encuentra en el folio 32.
- El memorial de fecha 31/05/2001 mediante el cual se allegan las copias de las solicitudes originales mediante las cuales se reivindica prioridad Británica UK0000313.7 de 10/01/2000 y UK0008837.7 de 12/04/2000 en los folios 57 a 67 y 84 a 94, junto con sus traducciones correspondientes en los folios 68 a 83 y 95 a 110.
- La solicitud de examen de patentabilidad junto con el pago de la tasa correspondiente en los folios 113 y 114.
- El requerimiento de Información técnica, efectuado a la luz del artículo 46 de la Decisión 486, que se encuentra en los folios 116 y 117.
- La respuesta al requerimiento técnico, allegada mediante memorial de fecha 22/08/2006, que se encuentra en los folios 118 a 124.

2. OBJETO DE LA INVENCION

La solicitud hace referencia a una ***“Formulación farmacéutica de liberación sostenida adaptada para administración por inyección”***.

- **Reivindicación 1:**

Se reivindica una formulación farmacéutica que comprende fulvestrat en un vehículo de oleato de ricino, un solvente éster no acuoso farmacéuticamente aceptable y un alcohol farmacéuticamente aceptable donde la formulación está adaptada para administración intramuscular y la obtención de una concentración fulvestrant en plasma sanguíneo, durante por lo menos 2 semanas.

- **Reivindicaciones 2 y 3:**

Se reclama una formulación farmacéutica adaptada para inyección intramuscular que comprende fulvestrant, 30% p/v o menos de un alcohol, 1% p/v de un solvente éster no acuoso miscible en oleato de ricino y una cantidad suficiente de un vehículo de oleato de ricino para preparar una formulación que es capaz después de inyectarse y de lograr una concentración de fulvestrant de por lo menos $2,5\text{mgml}^{-1}$ durante por lo menos 2 semanas.

- **Reivindicaciones 4 a 16:**

Se reivindica una formulación farmacéutica adaptada para inyección intramuscular que comprende fulvestrant, 30% p/v de un alcohol farmacéuticamente aceptable, 1% de un solvente éster no acuoso farmacéuticamente miscible en un vehículo de oleato de ricino y una cantidad suficiente de un vehículo de oleato de ricino en forma tal para preparar una formulación de por lo menos $4,5\text{mgml}^{-1}$ de fulvestrant.

En particular las formulaciones que contiene 25%p/v o menos ó 20% o menos de un alcohol farmacéuticamente aceptable y 60% p/v o menos ó 50% o menos ó 45% o menos ó 40% o menos ó 35% o menos , 30% ó menos ó 25% o menos de un solvente éster no acuoso farmacéuticamente aceptable.

Se reclaman las formulaciones en las que el alcohol farmacéuticamente aceptable es una mezcla de etanol y alcohol bencílico y el solvente éster no acuoso se selecciona a partir de bencil-benzoato, etil-oleato, Isopropil-miristato, Isopropil-palmitato o una mezcla de cualquiera de ellos, pero en particular es bencil-benzoato.

- **Reivindicación 17:**

Se reclama una formulación farmacéutica donde el volumen total de la formulación es 6ml o menos y la concentración de fulvestrant es por lo menos de 45mgml^{-1} .

- **Reivindicaciones 18 y 19:**

Se reclama una formulación farmacéutica donde la cantidad de fulvestrant en la formulación es 250mg o más y el volumen total de la formulación es 6ml o menos.

En particular se reclaman las formulaciones en las que la cantidad total de fulvestrant en la formulación es de 250mg y el volumen total de la formulación es 5 a 5,25ml.

Una vez catalogada la invención ésta se clasificó en la sección: A 61 K ³¹/₀₀₅ de la Clasificación Internacional de Patentes.

3. CLARIDAD DE LA SOLICITUD:

El artículo 30 de la Decisión 486 contempla que *"Las reivindicaciones definirán la materia que se desea proteger mediante la patente. Deben ser claras y concisas y estar enteramente sustentadas por la descripción"*.

Una vez efectuado el estudio del capítulo reivindicatorio, allegado a esta Dependencia con motivo de la solicitud de patente en cuestión, se señalan algunas objeciones de carácter formal que generan una falta de claridad del alcance de protección reclamado:

- Para esta Dependencia no es claro por qué se han incluido tres reivindicaciones independientes dentro del capítulo reivindicatorio (1,2 y 4), siendo que no comprenden materia adicional a la invención o un objeto diferente a la formulación descrita en la cláusula 1. Es por ello que se recomienda al interesado redactar el capítulo reivindicatorio considerando las dependencias entre una y otra cláusula.

5. DETERMINACIÓN DEL ESTADO DE LA TÉCNICA:

Consultadas las fuentes de información con que cuenta este despacho, se encontraron los siguientes documentos, anteriores a la fecha de presentación de la solicitud en estudio - 10.01.2000 -, relacionados con la materia técnica reivindicada:

Nº	Documento	Título	Fecha de Publicación
D1	XP-000998289*	"A case of Adenomyosis in a pigtailed monkey diagnosed by magnetic resonance imaging and treated with the novel pure antiestrogen, ICI 182,780"	June 1993
D2	Artículo 2**	"Pharmacokinetics, pharmacological and anti-tumor effects of the specific anti-oestrogen ICI 182780 in women with advanced breast cancer"	July 1996
D3	EP0346014	"Therapeutic product"	13/12/1989
D4	WO9721440	"A solution for oral administration containing ICI 182,780"	19/06/1997

*Artículo 1. Waterton J., Breen S., Dukes M., Horrocks M., Wadsworth P. "A case of Adenomyosis in a pigtailed monkey diagnosed by magnetic resonance imaging and treated with the novel pure antiestrogen, ICI 182,780", American Association for Laboratory Animal Science. Vol. 43, No. 8. June 1993. p247-251. XP-000998289.

**Artículo 2. Howell A., DeFriend DJ., Robertson JF., Blamey RW., Anderson L., Sutcliffe FA., Walton P. "Pharmacokinetics, pharmacological and anti-tumor effects of the specific anti-oestrogen IC 182780 in women with advanced breast cancer". British Journal of Cancer. 74(2): 300-8 July 1996.

Anterioridades D1, D2, D3 y D4 en los folios 120 a 124 y 129 a 138.

6. EVALUACIÓN DE LOS REQUISITOS DE PATENTABILIDAD:

El artículo 14 de la decisión 486 de la comisión de la comunidad andina establece que: *"Los países miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"*

En cumplimiento del artículo 14 de la decisión 486 de la comisión de la comunidad andina, se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

6.1 Evaluación del NIVEL INVENTIVO:

El artículo 18 de la decisión 486 dispone *"Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la Materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica"*

En atención al alcance de las anterioridades relacionadas D1, D2, D3 y D4 es evidente que el compuesto objeto de la composición que reclama la presente invención, era ampliamente conocido en el ámbito clínico desde la década de los 90's, y es en atención a ese conocimiento de la molécula que se desarrollaron diversas composiciones farmacéuticas utilizando los conocimientos que una persona versada en la materia técnica adquiere sobre excipientes farmacéuticos y las experiencias que formulaciones como las contempladas en las anterioridades D3 y D4 ya enseñaban sobre el comportamiento de la molécula en diversos sistemas de entrega.

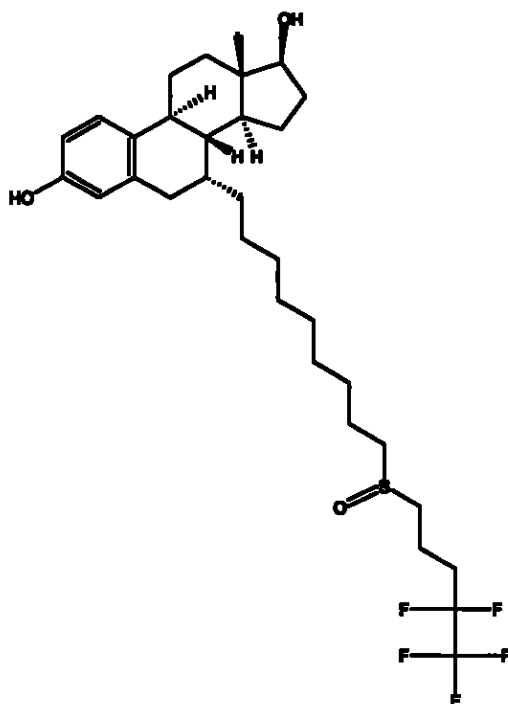


Ilustración 1. Fulvestrant

La anterioridad D4 muestra composiciones farmacéuticas diversas de Fulvestrant en sistemas de administración oral, pero es en realidad la anterioridad D3 la que contempla la posibilidad de una forma de dosificación desarrollada en aceite de ricino y alcohol bencílico para administración Intramuscular, fórmula que al compararse

directamente con la materia en estudio resulta una herramienta fundamental para que a partir de ella se desarrolle la fórmula reivindicada:

Fulvestrant, Ricin-oleato, Etanol, Alcohol bencílico, Benzoato de bencilo

Así las cosas, aunque el interesado acompañe dentro de su capítulo reivindicatorio todo un estudio de solubilidad de la molécula Fulvestrant en diferentes solventes – folio 11 -, resulta claro que ya en el estado de la técnica existía la suficiente información sobre el comportamiento de la molécula en diversos sistemas, dadas las enseñanzas que los documentos D3 y D4 contemplaban ya sobre formas de dosificación para administración oral e Intramuscular.

Siendo que el interesado es claro en afirmar que el problema consistía en la imposibilidad de administrar a un paciente más de 5 ml en una sola dosis de Fulvestrant en aceite de ricino, es claro que la anterioridad D3 ya señalaba los primeros pasos para contrarrestar los problemas de administración mediante la utilización de un solvente adicional en el sistema como el alcohol bencílico.

Ahora bien, si se tienen en cuenta las enseñanzas de los documentos D1 y D2 por sí solos, es evidente que sobre la farmacocinética de la molécula en sistemas de inyección por vía intramuscular y de sus efectos farmacológicos existía el suficiente conocimiento técnico, pero definitivamente es el documento D3 el que da las pautas para diseñar un sistema de solventes que permitiera administrar el compuesto, en consecuencia, sólo con las enseñanzas de este documento - D3 - es posible diseñar un vehículo farmacéutico que permita administrar el compuesto en la concentración requerida y en el volumen máximo permitido, basta con los conocimientos que una persona versada en ciencias farmacéuticas pudiese aplicar y basándose en los resultados contemplados en D3 para direccionar un proceso de preformulación que contemplase un solvente adicional para aumentar la solubilidad del compuesto en el sistema de entrega.

De otro lado, dentro del aparte descriptivo no se comparan las ventajas clínicas de la fórmula desarrollada con respecto al arte más cercano y que se encontraban en el estado de la técnica con antelación a la fecha de presentación de la solicitud en estudio, así las cosas, siendo que el desarrollo de la fórmula no es producto de una verdadera actividad inventiva, esta Dependencia encuentra que no se ha cumplido a cabalidad este requisito para que sea patentable el objeto reivindicado.

En conclusión los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	XP-000998289	1 a 19	Nivel Inventivo
D2	Artículo 2	1 a 19	Nivel Inventivo
D3	EP0348014	1 a 19	Nivel Inventivo
D4	WO9721440	1 a 19	Nivel Inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días

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contados a partir de la fecha de la notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo 5 del título primero de la Circular Única N° 10 de 2001

Alix Carmenza Céspedes de Vergel
Jefe de la División de Nuevas Creaciones

14 SET. 2006

El anterior requerimiento fue notificado por fijación en lista, de fecha _____

CONCEPTO TÉCNICO Número 01422	EXAMINADOR TÉCNICO Código 202044
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