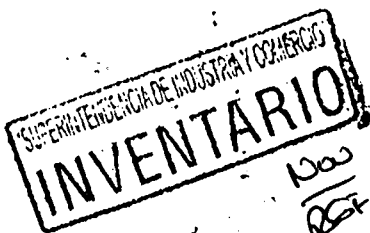




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Industria y Comercio

SUPERINTENDENCIA



PCT

SOLICITUD

PATENTE DE INVENCION

03-40570

1. EXPEDIENTE N°

4. TÍTULO *Uso de antiprogesterinas para la profilaxis y el tratamiento de enfermedades dependientes de hormonas.*

51. CLASIFICACIÓN INTERNACIONAL *A61K 31/56*

SOLICITANTE *Schering Aktiengesellschaft*

DOMICILIO *Berlin, Alemania*

74. APODERADO *Gustavo Hollmann Restrepo*

22. BOGOTÁ, D. C. *15 de mayo de 2003*
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① SOLICITUD DE :
☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.
☐ Capítulo I. ☒ Capítulo II.

② SOLICITANTE (71)	Nombre: SCHERING AKTIENGESELLSCHAFT	IDENTIFICACIÓN	
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⑤ PCT (86)
 Solicitud Internacional No. PCT/EP01/12005 Fecha Octubre 17 de 2001
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⑥ Título (54) **"USO DE ANTIPROGESTINAS PARA LA PROFILAXIS Y EL TRATAMIENTO DE ENFERMEDADES DEPENDIENTES DE HORMONAS".**

⑦ Clasificación Internacional (51) A61K 31/56

⑧ Prioridad SI ☒ NO ☐	(33) Pais de Origen <u>Europa</u> <u>Estados Unidos</u>	(32) Fecha <u>Octubre 18, 2000</u> <u>Octubre 18, 2000</u>	(31) Número de Solicitud <u>00250341.5</u> <u>60/240,998</u>

⑨ Comprobante de pago No. 33,176 y 33,187 Fecha Mayo 13, 2003

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

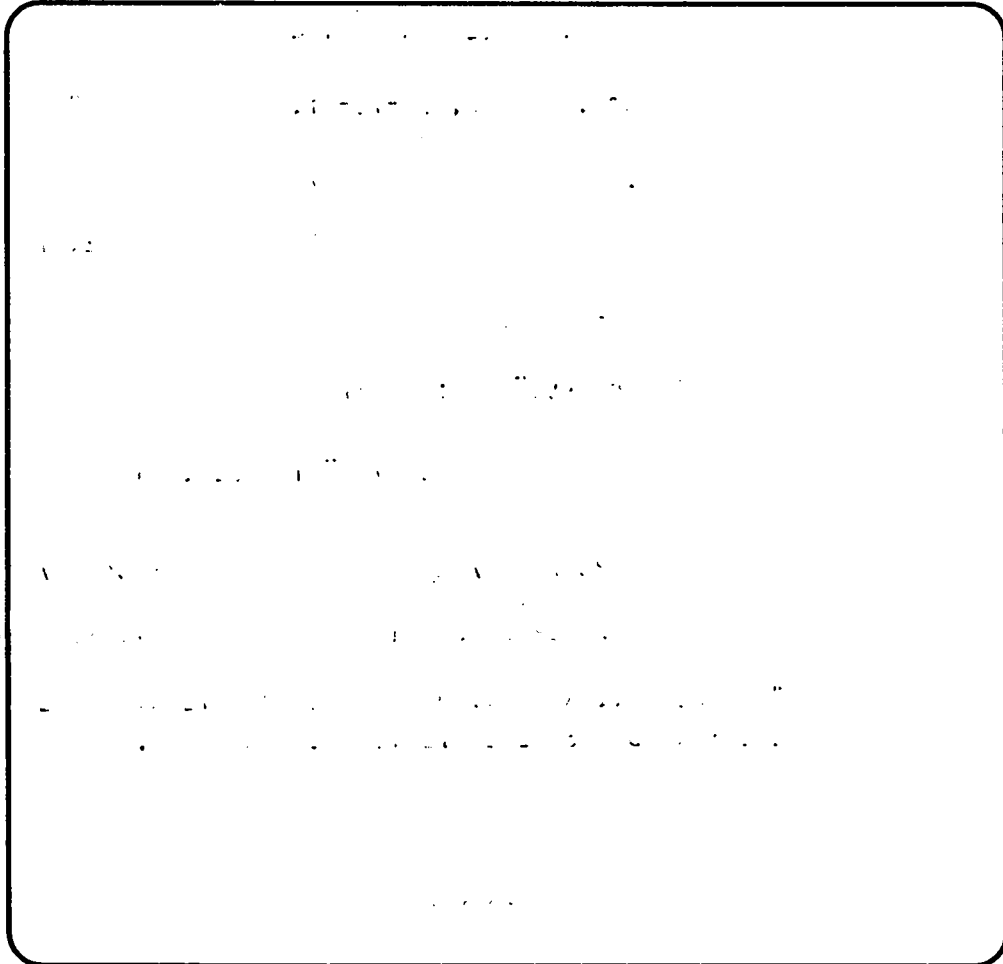
10

ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud.
- ☒ Documento que acredite la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso. **Protocolizado bajo el No. 605.**
- ☒ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
- ☒ Traducción del examen preliminar internacional efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico
- ☐ Arte final 12x12.
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☐ De ser el caso, modificaciones efectuadas a la solicitud internacional.
- ☒ Otros **Copia del Reporte de Búsqueda Internacional.**
- ☒ **Comprobante de pago de la tasa por Reivindicación de Prioridad.**

11

FIGURA CARACTERÍSTICA:



12

Solicito la concesión de la patente,

NOMBRE: **GUSTAVO HOLLMANN RESTREPO**

FIRMA:

C.C.

T.P.

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

Continuación enumeración del nombre de los Inventores, con
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SCHNEIDER, Martin	Schluchseestrasse 6a,	13469 Berlin, Alemania
FUHRMANN, Ulrike	Charlottenburger Ufer 6a,	10587 Berlin, Alemania

Otros anexos que se acompañan a la solicitud.

Copia notificación recepción copia registro (Forma PCT/IB/301)

Copia notificación de registro de un cambio (Forma PCT/IB/306)

Copia notificación entrega o transmisión certificado de prioridad (Forma PCT/IB/304)

Copia de notificación al solicitante sobre la comunicación de la solicitud internacional a las oficinas designadas (Forma PCT/IB/308).

Copia de la opinión escrita de la EPO del 29.04.2002

Contestación a la opinión escrita del 26.06.2002

Copia del petitorio.

4

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***** CONSIGNACION *****

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GUSTAVO HOLLMAN	CONSIGNACION	BANCO POPULAR	050-00110-6	11724172	13/05/2003	5,098,000.00

***** CONCEPTO *****

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

SON: CUATROCIENTOS MIL PESOS

RESPONSABLE : _____

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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES
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GUSTAVO HOLLMAN	CONSIGNACION	BANCO POPULAR	050-00110-6	11724172	13/05/2003	5,098,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	82 INVOCACION DE UNA PRIORIDAD EN NU	112,000.00
		TOTAL :	\$ 112,000.00

SON: CIENTO DOCE MIL PESOS

RESPONSABLE : _____

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(54) Title: USE OF ANTIPROGESTINS FOR PROPHYLAXIS AND TREATMENT OF HORMONE-DEPENDENT DISEASES

(57) Abstract: The present invention relates to methods and uses for preventing or treating hormone-dependent disease, in particular breast cancer, in a mammal by antiprogesterins, in particular antiprogesterin 11 β -(4-acetylphenyl)-17 β -hydroxy-17 α -(1,1,2,2,2-pentafluoroethyl)-estra-4,9-dien-3-one or a pharmaceutically acceptable derivative or analogue thereof. The invention further relates to pharmaceutical compositions comprising said antiprogesterin.

WO 02/32430 A1

USE OF ANTIPROGESTINS FOR PROPHYLAXIS AND TREATMENT OF HORMONE-DEPENDENT DISEASES

Field of the Invention

The present invention relates to the use of antiprogestins for the prophylaxis and treatment of hormone-dependent diseases, in particular breast cancer. The present invention further relates to pharmaceutical compositions and dosage forms comprising antiprogestins for the prophylaxis and treatment of hormone-dependent diseases, in particular breast cancer.

A particularly preferred antiprogesterin for use in the invention is the antiprogesterin 11β -(4-acetylphenyl)- 17β -hydroxy- 17α -(1,1,2,2,2-pentafluoroethyl)-estra-4,9-dien-3-one or a pharmaceutically acceptable derivative or analogue thereof.

Background of the Invention

Endocrine therapy represents a mainstay of effective, minimally toxic, palliative treatment for metastatic breast cancer. As a standard palliative treatment of non-operable mammary carcinomas as well as for adjuvant therapy after primary treatment of mammary carcinomas predominantly the antiestrogen tamoxifen is used. However, tamoxifen cannot cure breast cancer. Thus, for secondary therapy progestins or aromatase inhibitors are commonly used. In premenopausal women ovariectomy, tamoxifen and LHRH (luteinizing hormone releasing hormone) analogs achieve comparable results (H.T. Mouridsen et al., *Eur. J. Cancer Clin. Oncol.*, 24, pp. 99-105, 1988).

Although tamoxifen is widely used for adjuvant therapy of breast cancer, its use as a chemopreventive agent is problematic, because it has been shown that the treatment

results in an increase in the incidence of endometrial cancers (I.N. White, *Carcinogenesis*, 20(7):1153-60, 1999).

Antiprogestins represent a relatively new and promising class of therapeutic agents that
5 could have significant impact on breast cancer treatment. Although antiprogestins were
originally created with regard to medicinal non-surgical termination of pregnancy (EP 129
499), certain antiprogestins have recently gained importance in the endocrine therapy of
those breast cancers involving receptors for progesterone (T. Maudelonde et al., in: J.G.M.
Klijn et al., *Hormonal Manipulation of Cancer: Peptides, Growth Factors and New (Anti)*
10 *Steroid Agents*, Raven Press, New York, 1987, pp. 55-59). This new strategy in
endocrine therapy is based on the antitumor activity of antiprogestins in progesterone
receptor-positive human breast cancer cell lines *in vitro* and in several hormone-dependent
mammary tumors of the mouse and rat *in vivo*. In particular, the antitumor mechanism of
the antiprogestins onapristone and mifepristone (RU 486) was investigated using the
15 hormone-dependent MXT mammary tumor model of the mouse as well as the DMBA-
and the NMU-induced mammary tumor models of the rat (M. R. Schneider et al., *Eur. J.*
Cancer Clin. Oncol., Vol. 25, No. 4, pp. 691-701, 1989; H. Michna et al., *Breast Cancer*
Research and Treatment 14:275-288, 1989; H. Michna, *J. Steroid. Biochem.* Vol. 34, Nos
1-6, pp. 447-453, 1989). However, due to low activity and adverse side effects involved
20 with e.g. mifepristone this compound could not be recommended as a single agent in the
management of breast cancer (D. Perrault et al., *J. Clin. Oncol.* 1996 Oct, 14(10),
pp.2709-2712).

Antiprogesterin compounds are suitable for initiating abortions and thus for use in postcoital
25 fertility control, as contraceptives for women (WO-A 93/23020, WO-A 93/21927) and
further for the treatment of hormone irregularities, for initiating menstruation and for
initiating labor. Further indications are in the field of hormone substitution therapy (WO-
A 94/18983), the treatment of afflictions related to dysmenorrhea and the treatment of
endometriosis (EP-A 0 266 303) as well as myomas.
30 17 α -fluoroalkylsteroids having strong antiprogesterin activity as well as methods for
producing them are described in WO 98/34947.

Antiprogestins of the prior art tested or used previously due to their antitumor activity frequently exhibited certain disadvantages.

5 For example, despite the fact that prior art antiprogestins exhibited antigestagenic activity, these compounds were not suitable treatments for hormone-dependent diseases such as breast cancer. In particular, prior art compounds were associated with side effects, e.g. mifepristone exhibits strong antiglucocorticoid side effects (cf. L.M. Kettel et al., *Fertil. Steril.* 1991 Sep, 56(3), pp. 402-407; X. Bertagna, *Psychoneuroendocrinology* 1997; 22
10 Suppl. 1, pp. 51-55) and besides it showed only moderate activity in clinical trials (see again D. Perrault et al., *J. Clin. Oncol.* 1996 Oct, 14(10), pp.2709-2712). Regarding side effects of other hormone-based therapies, as already mentioned above, tamoxifen administration can result in an increase in the incidence of endometrial cancers (I.N. White, *Carcinogenesis*, 20(7):1153-60, 1999).

15

Another problem with prior art antiprogestins was poor bioavailability when administered orally. Thus, they generally had to be administered in high doses, giving rise to possible unfavorable side effects. Moreover, oral administration is desirable with respect to patient convenience and compliance.

20

Furthermore, there is still a need for compounds that are active not only in the treatment, but also in the prophylaxis of breast cancer and other hormone-dependent diseases. The increased incidence of endometrial cancer associated with tamoxifen tends to show that this compound is unsuitable for prophylaxis treatment of healthy women, and no other
25 suitable compounds are available (cf. L. Bergman et al., *The Lancet*, Vol. 356, Sept. 9, 2000; 881-887).

30 Object of the Present Invention

It is an object of the present invention to prevent or reduce the disadvantages of the prior art methods for preventing or treating hormone-dependent diseases, such as breast cancer. It is especially desired that a means of preventing and treating hormone-dependent diseases, such as breast cancer, via the administration of highly effective agents is provided that is superior to known methods and agents, including ovariectomy. Thus it is further especially desired to provide a treatment of hormone-dependent diseases, such as breast cancer, that prevents serious and risk-laden surgery involved with ovariectomy. It is further desired to provide an agent for use according to the invention exhibiting less side effects than previously known or suggested methods for treating and preventing hormone-dependent diseases such as breast cancer.

It is a further object of the present invention to provide pharmaceutical compositions comprising highly effective antitumor agents for the prophylaxis and treatment of breast cancer and other hormone-dependent diseases.

These objects are surprisingly achieved by the use of antiprogestins according to the present invention and by pharmaceutical compositions and dosage forms comprising such antiprogestins. Particularly preferred in this regard is the antiprogestin 11β -(4-acetylphenyl)- 17β -hydroxy- 17α -(1,1,2,2,2-pentafluoroethyl)-estra-4,9-dien-3-one or a pharmaceutically acceptable derivative or analogue thereof.

It is a further object of the present invention to provide antiprogestins, such as the antiprogestin 11β -(4-acetylphenyl)- 17β -hydroxy- 17α -(1,1,2,2,2-pentafluoroethyl)-estra-4,9-dien-3-one or pharmaceutically acceptable derivatives or analogues thereof, that are particularly suitable for oral administration.

Summary of the Invention

The present invention is based on the novel and unexpected observation that certain antiprogestins, in particular 11β -(4-acetylphenyl)- 17β -hydroxy- 17α -(1,1,2,2,2-pentafluoroethyl)-estra-4,9-dien-3-one or a pharmaceutically acceptable derivative or analogue thereof, are exceptionally active in the prevention and reduction of tumor growth

in DMBA (7,12-dimethylbenzanthracene)- and NMU (N-methylnitrosourea)-induced breast cancer models. In fact, the antiprogesterin 11β -(4-acetylphenyl)- 17β -hydroxy- 17α -(1,1,2,2,2-pentafluoroethyl)-estra-4,9-dien-3-one (I) turned out to be distinctly more potent than tamoxifen and ovariectomy in the prevention of breast cancer development.

5

Thus, the present invention provides a method for prophylaxis and treatment of breast cancer and other hormone-dependent diseases in mammals, in particular humans, in need of such treatment, said method comprising administering a pharmaceutically effective amount of an antiprogesterin, in particular 11β -(4-acetylphenyl)- 17β -hydroxy- 17α -(1,1,2,2,2-pentafluoroethyl)-estra-4,9-dien-3-one, or a pharmaceutically acceptable derivative thereof or analogue thereof, to a patient.

10

The present invention further provides pharmaceutical compositions comprising an antiprogesterin, in particular 11β -(4-acetylphenyl)- 17β -hydroxy- 17α -(1,1,2,2,2-pentafluoroethyl)-estra-4,9-dien-3-one or a pharmaceutically acceptable derivative or analogue thereof, in an amount sufficient for the prophylaxis or treatment of breast cancer or other hormone-dependent diseases.

15

The preferred antiprogesterin 11β -(4-acetylphenyl)- 17β -hydroxy- 17α -(1,1,2,2,2-pentafluoroethyl)-estra-4,9-dien-3-one will hereinafter be referred to as "antiprogesterin (I)".

20

Brief Description of the Figures

Figure 1 shows the tumor development prevention effect of antiprogesterin (I) in the DMBA-induced mammary carcinoma of the rat, compared with a control, tamoxifen and ovariectomy.

25

Figure 2 shows the tumor growth inhibiting effects of antiprogesterin (I) in a dose-response study in the DMBA-induced mammary carcinoma of the rat, compared with a control, the antiprogesterin onapristone as well as ovariectomy. The study was performed with 0.5, 2.0, 5.0 and 10.0 mg/kg s.c. doses of antiprogesterin (I).

30

Figure 3 shows the tumor development prevention effect of antiprogesterin (I) in the NMU-induced mammary carcinoma of the rat, compared with a control, the antiestrogens raloxifen and tamoxifen, the aromatase inhibitor letrozol as well as ovariectomy.

5

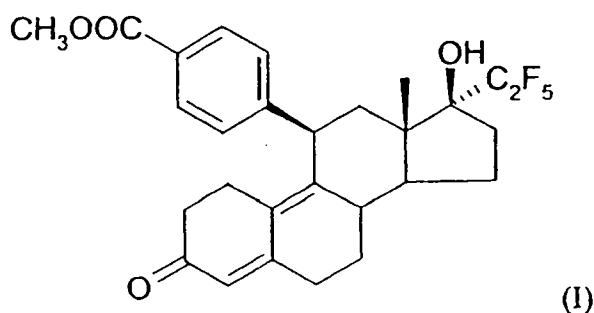
Figure 4 shows the tumor growth inhibiting effect of 0.5 and 1.0 mg/kg doses of antiprogesterin (I) in the NMU-induced mammary carcinoma of the rat, compared with a control, onapristone (5 mg/kg) and ovariectomy.

10. Figure 5 shows the tumor growth inhibiting effect of antiprogesterin (I) in a 10 mg/kg s.c. dose in the T47D human xenograft in scid mice, compared to a control as well as ovariectomy.

15 Figure 6 shows the tumor growth inhibiting effect of antiprogesterin (I) in a 10 mg/kg s.c. dose in the MCF7 human xenograft in scid mice, compared to a control as well as ovariectomy.

Detailed Description of the Invention

20 Antiprogesterin (I) — 11 β -(4-acetylphenyl)-17 β -hydroxy-17 α -(1,1,2,2,2-pentafluoroethyl)-estra-4,9-dien-3-one — is represented below by formula (I):



25 Antiprogesterin (I) (or a pharmaceutically acceptable derivative or analogue thereof having comparable activity) is a valuable pharmaceutical agent having strong antiprogesterin activity. Antiprogesterin (I), as well as further antiprogesterins, can be used according to the

present invention for the prophylaxis and treatment of breast cancer and other hormone-dependent diseases.

The term "antiprogestin" in the context of the present invention is intended to primarily
5 comprise all compounds being capable of competitively inhibiting progesterone receptors.
However, it should also encompass compounds capable of inhibiting the biosynthesis of
progestins.

A pharmaceutically acceptable derivative or analogue of antiprogestin (I) in the context of
10 the present invention may include, for example, any one of the inventive compounds
disclosed in WO 98/34947.

The term "hormone-dependent diseases" in the context of the present invention may
include, but is not limited to, breast cancer, ovarian cancer, endometrial cancer, myeloma,
15 anovulatory infertility, meningoma, i.e. diseases which substantially originate or are
influenced by the presence of hormone receptors and/or hormone-dependent pathways.

As regards the superiority of the present invention over the prior art, it is especially
favorable that, e.g., in antiprogestin (I) used according to the present invention further
20 endocrine side effects, such as e.g. androgen, estrogen or antiglucocorticoid activity are
only very weak, if present at all. Due to the high bioavailability of antiprogestin (I) it can
be administered orally, thus rendering the treatment for a patient in need thereof as
convenient as possible. As a further favorable consequence, antiprogestin (I) is well
tolerated and can be administered in relatively low doses compared to established
25 treatments thus reducing undesirable side effects, such as an increase in the incidence of
endometrial cancers with the administration of tamoxifen (see I.N. White, *Carcinogenesis*,
20(7):1153-60, 1999; L. Bergman et al., *The Lancet*, Vol. 356, Sept. 9, 2000, 881-887) as
well as the antiglucocorticoid effects and certain toxic side effects related to the
administration of mifepristone (see D. Perrault et al., *J. Clin. Oncol.* 1996 Oct, 14(10),
30 pp.2709-2712; L.M. Kettel et al., *Fertil. Steril.* 1991 Sep, 56(3), pp.402-407; X. Bertagna,
Psychoneuroendocrinology 1997, 22 Suppl. 1; pp. 51-55).

A further advantage of the present invention over the prior art is the provision of an effective method for the prophylaxis of hormone-dependent diseases such as breast cancer, such that patients under high risk of developing or re-developing hormone-
5 dependent diseases can be treated in advance to avoid incidence of such diseases.

In a first aspect the present invention relates to a method for the prophylaxis or treatment of breast cancer and other hormone-dependent diseases, comprising administering at least one antiprogestin, preferably antiprogestin (I) or a pharmaceutically acceptable derivative
10 or analogue thereof to a mammal, preferably a human, in need of such prophylaxis or treatment.

In a further aspect the present invention relates to the use of antiprogestins as defined above, preferably antiprogestin (I) or a pharmaceutically acceptable derivative or analogue
15 thereof, for the manufacture of a medicament, in particular for the prophylaxis or treatment of breast cancer or other hormone-dependent diseases.

In another aspect the present invention relates to pharmaceutical compositions comprising at least one antiprogestin as defined above, preferably antiprogestin (I) or a
20 pharmaceutically acceptable derivative or analogue thereof. Optionally the antiprogestin (I) can be combined with other pharmacologically active agents. For example, the antiprogestin may also be combined with a cytotoxic agent for treatment by coupling to a hormone receptor.

25 The manufacture of the medicaments may be performed according to methods known in the art. Commonly known and used adjuvants as well as further suitable carriers or diluents may be used. Suitable carriers and adjuvants may be such as recommended for pharmacy, cosmetics and related fields in: *Ullmann's Encyclopedia of Technical Chemistry*, Vol. 4, (1953), pp. 1-39; *Journal of Pharmaceutical Sciences*, Vol. 52 (1963),
30 p. 918ff; H.v.Czetsch-Lindenwald, "Hilfsstoffe für Pharmazie und angrenzende Gebiete";

Pharm. Ind. 2, 1961, p.72ff, Dr. H.P. Fiedler, *Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete*, Cantor KG, Aulendorf in Württemberg, 1971.

Antiprogestins suitable for the purposes of the present invention, preferably antiprogestin
5 (I) or a pharmaceutically acceptable derivative or analogue thereof, can be incorporated into pharmaceutical compositions according to known methods of preparing galenics for oral or parenteral, e.g., intraperitoneal, intramuscular, subcutaneous or percutaneous application. They can also be implanted into tissue. Implants can comprise as inert materials e.g. biologically degradable polymers or synthetic silicones such as e.g. silicone
10 rubber.

They can be administered in the form of tablets, pills, dragees, gel capsules, granules, suppositories, implants, injectable sterile aqueous or oily solutions, suspensions or
15 emulsions, ointments, creams, gels or by intravaginal (e.g., vaginal rings) or intrauterine systems (e.g., diaphragms, loops).

For the preparation of pharmaceutical compositions for oral administration, the antiprogestins suitable for the purposes of the present invention as defined above can be
20 admixed with commonly known and used adjuvants and carriers such as for example, gum arabic, talcum, starch, sugars such as, e.g., mannitose, methyl cellulose, lactose, gelatin, surface-active agents, magnesium stearate, aqueous or non-aqueous excipients, paraffin derivatives, cross-linking agents, dispersants, emulsifiers, lubricants, conserving agents and flavoring agents (e.g., ethereal oils). In the pharmaceutical composition, the antiprogestin may be dispersed in a microparticle, e.g. a nanoparticulate, composition.

25 In order to further enhance the bioavailability of the active agent, the antiprogestins suitable for the purposes of the present invention as defined above can also be formulated as cyclodextrin clathrates by reacting them with α -, β - or γ -cyclodextrines or derivatives thereof according to the method as disclosed in PCT/EP95/02656.

For parenteral administration the antiprogestins suitable for the purposes of the present invention as defined above can be dissolved or suspended in a physiologically acceptable diluent, such as, e.g., oils with or without solubilizers, surface-active agents, dispersants or emulsifiers. As oils for example and without limitation, olive oil, peanut oil, cottonseed
5 oil, soybean oil, castor oil and sesame oil may be used.

The amount to be administered (i.e., a "pharmaceutically effective amount") varies within a broad range and depends on the condition to be treated and the mode of administration.

It can cover any amount efficient for the intended treatment. Determining a
10 "pharmaceutically effective amount" is within the purview of the person skilled in the art.

One unit dose may represent about 0.1 to 100 mg active agent(s). For administration to humans, the daily dose of the active agent(s) is about 0.1 to 400 mg, preferably 10 to 100 mg, most preferably 50 mg.

15

The pharmaceutical compositions according to the present invention can also be administered via a depot injection, an implant preparation or an IUD (internal uterine device), optionally for sustained delivery of the active agent(s).

20 The preferred mode of administration is oral administration. The antiprogestins for use according to the invention, and in particular, antiprogestin (I) or a pharmaceutically acceptable derivative or analogue thereof are particularly suitable for oral administration.

According to all aspects of the present invention it is also possible to combine at least one
25 antiprogestin as defined above, in particular antiprogestin (I) or a pharmaceutically acceptable derivative or analogue thereof, with at least one antiestrogen, because many hormone-dependent diseases, in particular breast cancer, exhibit not only progesterone receptors, but also estrogen receptors. The antiestrogen may be administered either simultaneously with or sequentially to the antiprogestin, and in particular with/to
30 antiprogestin (I) or a pharmaceutically acceptable derivative or analogue thereof. The amount of antiprogestin and antiestrogen may be equal or one component may be more

predominant than the other, such as in an antiprogesterin:antiestrogen ratio of 1:50 to 50:1, preferably 1:30 to 30:1, and most preferably 1:15 to 15:1.

Examples of suitable antiestrogens for use according to the invention are non-steroidal antiestrogens, such as tamoxifen and nafoxidine as well as raloxifen and EM800 and the steroidal antiestrogen faslodex. Examples of steroidal antiestrogens include those disclosed in EP 0 348 341 A and those disclosed in WO 98/07740, in particular, 11 β -flouro-7 α -{5-[N-methyl-N-3-(4,4,5,5,5-pentafluoropentylthio-propylamino)-pentyl]-estra-1,3,5(10)-trien-3,17 β -diol, or those disclosed in WO 99/33855, in particular 11 β -flouro-7 α -{5-[methyl-(7,7,8,8,9,9,10,10,10-nonafluoro-decyl)-amino]-pentyl]-estra-1,3,5(10)-trien-3,17 β -diol or pharmaceutically acceptable derivatives or analogues thereof. Aromatase inhibitors having an antiestrogenic effect, such as those disclosed on pages 7 to 8 of EP 0 495 825 B1 may also be used as antiestrogens.

The invention is further illustrated in the examples. The following examples are not to be understood as a limitation.

Examples

20 Example 1:

DMBA-induced breast cancer model in rat (prevention experiment)

Materials and Methods:

25 Immature female Sprague-Dawley rats (49 - 51 days old; 10 animals/group) were used in this study. The carcinogen 7,12-dimethylbenz[a]anthracene (DMBA) was given as a single oral administration (10 mg). Treatment was started 20 days later as followed: 1) solvent control, 2) ovariectomy at treatment start, 3) tamoxifen, 1 mg/kg s.c., 4) antiprogesterin (I), 3 mg/kg, s.c., 6 days/week. Rats were examined weekly for breast
30 tumors by palpation. As a parameter for the prophylactic effect the tumor incidence (number of animals/group with tumors in %) was determined. For a further description

and evaluation of DMBA and NMU prevention models, see R.G. Metha, *European Journal of Cancer* 36 (2000), pp. 1275-1282.

Results:

5

In the control group all rats developed mammary tumors within 10 weeks after treatment start (incidence 100%) and progressive tumor growth was observed. Prophylactic treatment with the antiprogesterin (I) prevented the tumor development for 12 weeks completely, and at the end of the experiment, after 22 weeks, in only one rat a tumor was
10 detected (incidence 10%). After ovariectomy at the end of the experiment 40% of the rats had developed tumors. In comparison, treatment with the antiestrogen tamoxifen reduced the tumor incidence only to 60% (see fig. 1)

Conclusion:

15

In the DMBA-induced mammary tumor model in the rat, the antiprogesterin (I) completely suppressed the tumor development in intact animals for more than 12 weeks after treatment start. Figure 1 clearly shows the superiority in activity of antiprogesterin (I) over the conventional anti-breast cancer reagent tamoxifen and even over standard estrogen
20 deprivation therapy (ovariectomy) with respect to prophylactic treatment. Antiprogesterin (I) is thus superior to the established standard therapy for preventing breast cancer in women under high risk of developing the disease (tamoxifen prophylactic therapy).

These and the following results indicate that the use of antiprogesterin (I) for the
25 prophylaxis and treatment of breast cancer is superior to established standard treatments.

30

Example 2:DMBA-induced breast cancer model in rat (therapy experiment/dose-response study)

Materials and Methods:

5

Immature female Sprague-Dawley rats (49 - 51 days old; 10 animals/group) were used in this study. Mammary tumors were induced by a single oral administration of 10 mg 7,12-dimethylbenz[a]anthracene (DMBA, Serva/Heidelberg). Rats with at least one established

10 tumor with a size of more than 150 mm² were treated for 4 weeks by: 1) solvent control, 2) ovariectomy at treatment start, 3) antiprogesterone (I), 0.5 mg/kg s.c., 4) antiprogesterone (I), 2 mg/kg s.c., 5) antiprogesterone (I), 5 mg/kg s.c., 6) antiprogesterone (I), 10 mg/kg s.c., and 7) onapristone, 5 mg/kg, s.c., daily. As a parameter for growth inhibition the change of tumor area (in % with respect to initial tumor size) determined by weekly caliper measurements was used. For statistical analysis of intergroup differences of mean values the Kruskal-
15 Wallis-test was used.

Results:

In intact control animals, progressive tumor growth was observed, whereas ovariectomy
20 caused a considerable tumor regression in 90% of the animals. Treatment with antiprogesterone (I) at doses of or above 2 mg/kg resulted in a significant inhibition of tumor growth compared with the control (see fig. 2). There was a clear dose-response relationship. Whereas treatment with 0.5 mg/kg antiprogesterone (I) did not significantly prevent the tumor from growing, at 2 mg/kg maximal growth inhibition was observed. In
25 this group a complete tumor regression was seen in 50% of the rats. The effect of the highest dose of antiprogesterone (I) tested in this experiment (10 mg/kg), was comparable to that of 2 mg/kg. Onapristone (5 mg/kg, s.c.) was distinctly less effective than antiprogesterone (I) at comparable doses.

30

Conclusion:

In the DMBA-induced mammary tumor model in the rat, antiprogesterin (I) completely suppresses the tumor growth in intact animals. It was found that 2 mg/kg antiprogesterin (I) has a maximal effect on tumor growth. Antiprogesterin (I) was distinctly superior to onapristone.

Example 3:

10 NMU-induced breast cancer model in rat (prevention experiment)

Materials and Methods:

Tumors were induced by a single intravenous injection of NMU (nitrosomethylurea, 50 mg/kg) in female Sprague-Dawley rats (obtained from Tierzucht Schönwalde, age 50-55 days). Treatment was started 10 days later as followed: 1) solvent control, 2) ovariectomy at treatment start, 3) tamoxifen, 3 mg/kg s.c., 4) antiprogesterin (I), 3 mg/kg, s.c., 5) letrozole, 3 mg/kg s.c., 6) raloxifen, 3 mg/kg s.c., 6 days/week. Rats were examined weekly for breast tumors by palpation. As a parameter for the prophylactic effect the tumor incidence (number of animals/group with tumors in %) was determined. For a further description and evaluation of DMBA and NMU prevention models, see R.G. Metha, *European Journal of Cancer* 36 (2000), pp. 1275-1282.

Results:

25

In the control group all rats developed mammary tumors within 10 weeks after treatment start (incidence 100%; see fig. 3) and progressive tumor growth was observed. Prophylactic treatment with the antiprogesterin (I) prevented the tumor development for 12 weeks completely, and at the end of the experiment, after 27 weeks, in only one rat a tumor was detected (incidence 10%). In comparison, in treatment with the other antiestrogens or the aromatase inhibitor letrozole the tumor incidence was reduced only to

30

20 - 60%. After ovariectomy at the end of the experiment 20% of the rats had developed tumors.

Conclusion:

5

In the NMU-induced mammary tumor model in the rat, antiprogesterin (I) completely suppressed the tumor development in intact animals for more than 12 weeks after treatment start. The effect of the prophylactic treatment by antiprogesterin (I) was superior to that of conventional antiestrogens for breast cancer therapy (i.e., raloxifen, tamoxifen) and aromatase inhibitor letrozol and to standard estrogen deprivation therapy (ovariectomy) regarding tumor incidence and tumor growth.

As in the DMBA-induced tumor model (see Example 1), these results indicate that antiprogesterin (I) effectively prevents the development of breast tumors in a manner which is superior to the standard prophylactic treatment, e.g. with tamoxifen.

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Example 4:

NMU-induced breast cancer model in rat (therapy experiment)

20

Materials and Methods:

Tumors were induced by a single intravenous injection of NMU (nitrosomethylurea, 50 mg/kg) in female Sprague-Dawley rats (obtained from Tierzucht Schönwalde, age 50-55 days). Starting 10 days later, rats with at least one established tumor were treated for 4 weeks by: 1) solvent control, 2) ovariectomy at treatment start, 3) antiprogesterin (I), 1.0 mg/kg/day, 4) antiprogesterin (I), 0.5 mg/kg/day and 5) onapristone, 5 mg/kg/day. As a parameter for growth inhibition the change of tumor area (in % of initial tumor size) determined by weekly caliper measurements was used. For statistical analysis of intergroup differences of mean values the Kruskal-Wallis-test was used.

30

Results:

In intact control animals, progressive tumor growth was observed, whereas ovariectomy caused a complete tumor growth inhibition. Treatment with antiprogesterin (I) at doses of 0.5 or 1.0 mg/kg resulted in a significant inhibition of tumor growth compared with the control (see fig. 4). Onapristone (5 mg/kg) was distinctly less effective than antiprogesterin (I) at the much lower dose of 0.5 mg/kg.

Conclusions:

In the MNU-induced mammary tumor model in the rat, antiprogesterin (I) completely suppresses the tumor growth in intact animals. It was found that at a dose of 1.0 mg/kg and even at a dose of only 0.5 mg/kg antiprogesterin (I) has a significant effect on tumor growth. Thus, antiprogesterin (I) was superior to known antiprogesterins like onapristone.

Example 5:

T47D Human xenograft (therapy experiment)

Materials and Methods:

Female Fox Chase scid mice (M&B) were supplemented with estradiol pellets (Innovative Research of America). T47D breast cancer cells, obtained from cell culture and suspended in matrigel, were implanted s.c. in the inguinal region of the mice. Treatment was started when the tumors were approximately 25 mm² in size. Treatment was continued until progression of the tumors. Experimental groups were: 1) control (vehicle), 2) ovariectomy, 3) antiprogesterin (I), 10 mg/kg s.c.. Tumor area was determined by caliper measurements. The Kruskal Wallis test was used for statistical analysis of intergroup differences of mean values.

Results:

In the T47D breast cancer model, ovariectomy resulted in a considerable inhibition of tumor growth, compared with the rapid growth in the control. Fig. 5 shows that the s.c. application of 10 mg/kg antiprogesterin (I) also caused an inhibition of tumor growth, almost comparable to the effect of conventional estrogen deprivation therapy (ovariectomy).

Conclusion:

The effect of antiprogesterin (I) in inhibiting the growth of the human T47D breast cancer xenografted in Fox Chase scid mice is comparable to the effect of standard estrogen deprivation therapy (ovariectomy) which is considered to be the maximum effective method of inhibiting growth of breast cancer in this model.

Example 6:

MCF7 Human xenograft (therapy experiment)

Materials and Methods:

Female Fox Chase scid mice (M&B) were supplemented with estradiol pellets (Innovative Research of America). MCF7 breast cancer cells, obtained from cell culture and suspended in matrigel, were implanted s.c. in the inguinal region of the mice. Treatment was started when the tumors were approximately 25 mm² in size. Treatment was continued until progression of the tumors. Experimental groups were: 1) control (vehicle), 2) ovariectomy, 3) antiprogesterin (I), 10 mg/kg s.c. Tumor area was determined by caliper measurements. The Kruskal Wallis test was used for statistical analysis of intergroup differences of mean values.

Results:

In the MCF7 breast cancer model, ovariectomy resulted in a considerable inhibition of tumor growth, compared with the rapid growth in the control. Fig. 6 shows that the s.c. application of 10 mg/kg antiprogesterin (I) also caused an inhibition of tumor growth, almost comparable to the effect of conventional estrogen deprivation therapy (ovariectomy).

Conclusion:

The effect of antiprogesterin (I) in inhibiting the growth of the human MCF7 breast cancer xenografted in Fox Chase scid mice is comparable to the effect of standard estrogen deprivation therapy (ovariectomy) which is considered to be the maximum effective method of inhibiting growth of breast cancer in this model.

CLAIMS

1. Use of the antiprogestin 11β -(4-acetylphenyl)- 17β -hydroxy- 17α -(1,1,2,2,2-pentafluoroethyl)-estra-4,9-dien-3-one or a pharmaceutically acceptable derivative or analogue thereof for the manufacture of a medicament for the prophylaxis or treatment of a hormone-dependent disease in a mammal.
2. Use according to claim 1, wherein the disease is breast cancer.
3. Use according to claims 1 or 2, wherein the mammal is a human.
4. Use according to any preceding claim, wherein the medicament is administered orally.
5. Use according to any preceding claim, wherein the antiprogestin 11β -(4-acetylphenyl)- 17β -hydroxy- 17α -(1,1,2,2,2-pentafluoroethyl)-estra-4,9-dien-3-one is administered in a unit dose of 50 mg.
6. Pharmaceutical composition comprising the antiprogestin 11β -(4-acetylphenyl)- 17β -hydroxy- 17α -(1,1,2,2,2-pentafluoroethyl)-estra-4,9-dien-3-one or a pharmaceutically acceptable derivative or analogue thereof in an amount sufficient for the prophylaxis or treatment of a hormone-dependent disease in a mammal.
7. Pharmaceutical composition according to claim 6, wherein the disease is breast cancer.

8. Pharmaceutical composition according to claims 6 or 7, wherein the mammal is a human.
 9. Pharmaceutical composition according to any one of claims 6 to 8, further comprising an antiestrogen.
- 5

FIG. 1

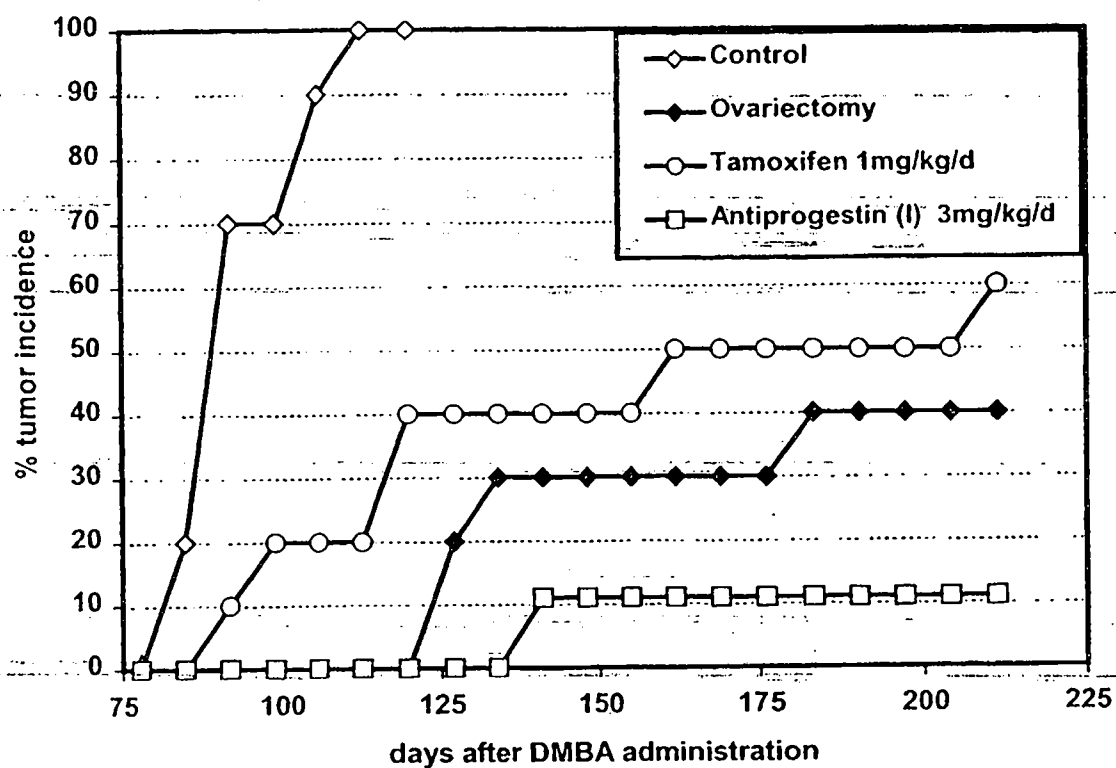


FIG. 2

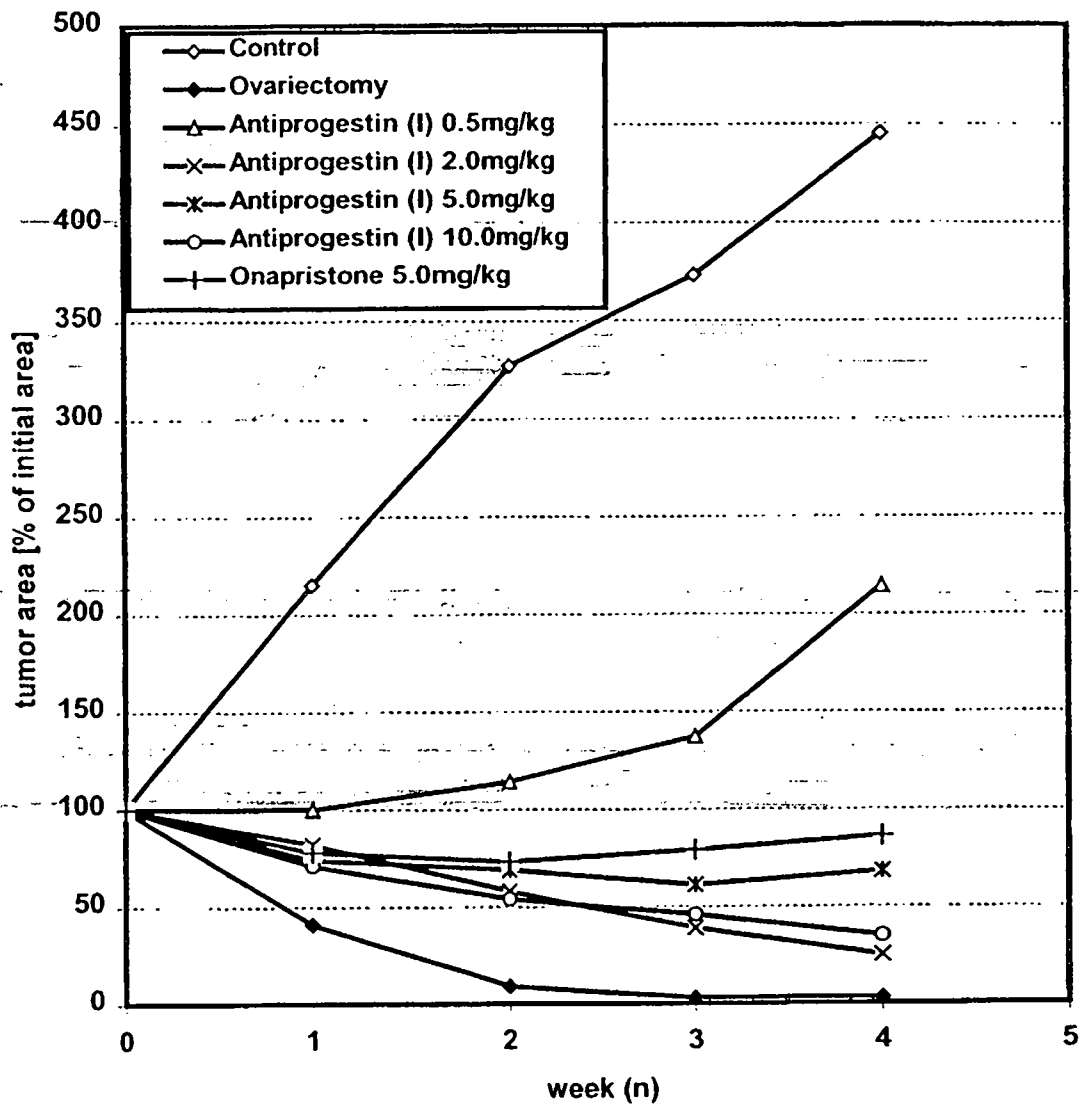


FIG. 3

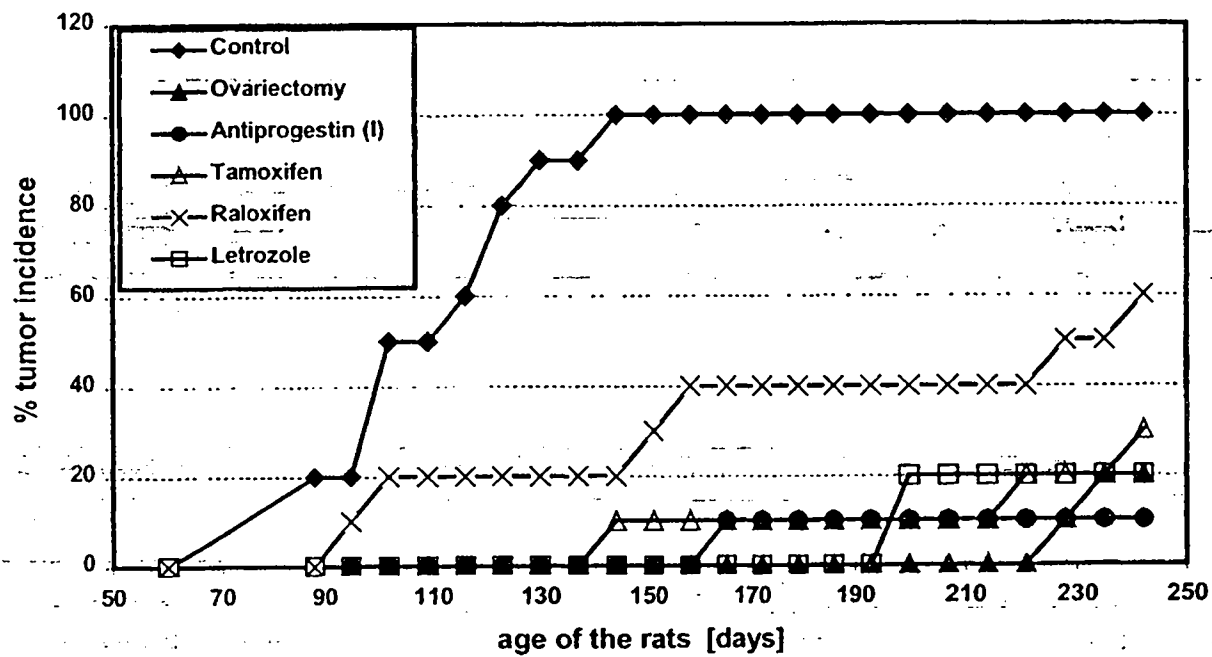


FIG. 4

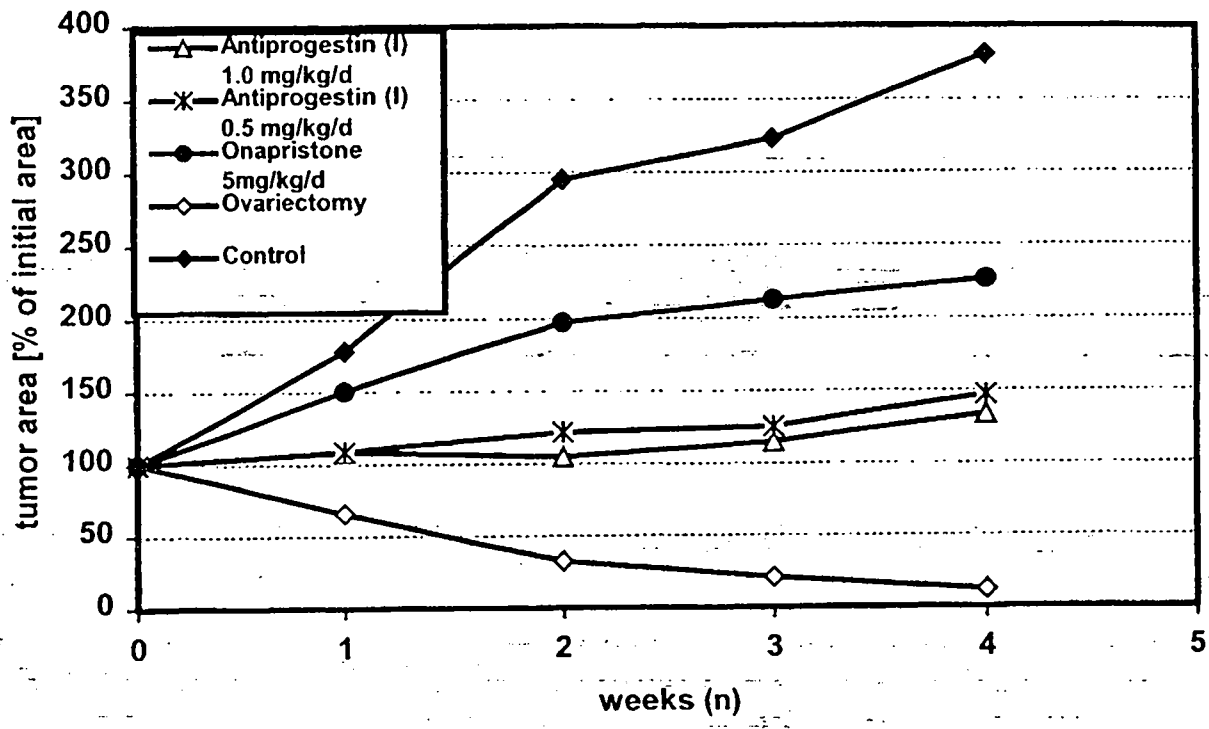


FIG. 5

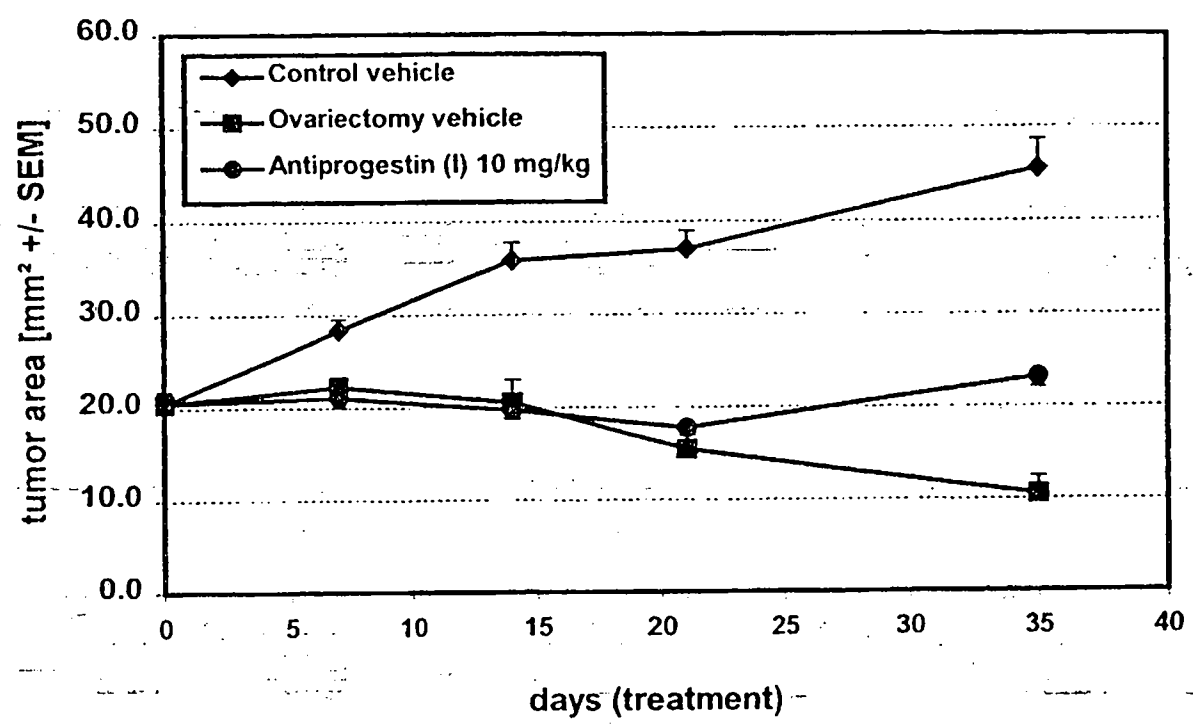
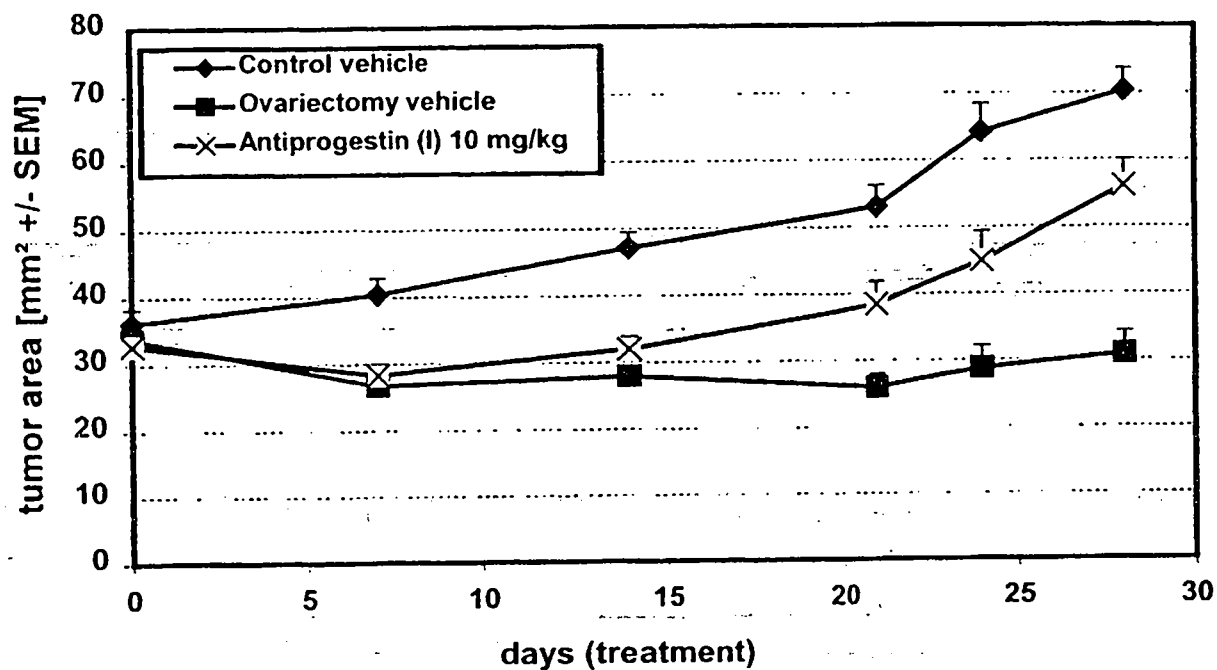


FIG. 6



INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 01/12005

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/56 A61P35/00

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)

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

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

EPO-Internal, WPI Data, PAJ, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT.

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 197 06 061 A (SCHERING AG) 13 August 1998 (1998-08-13) abstract; claims 1-22; example 3	1, 3-6, 8, 9
P, X	FUHRMANN ULRIKE ET AL.: "Synthesis and Biological Activity of a Novel, Highly Potent Progesterone Receptor Antagonist" JOURNAL OF MEDICINAL CHEMISTRY., vol. 43, no. 26, 7 December 2000 (2000-12-07), pages 5010-5016, XP001064233 AMERICAN CHEMICAL SOCIETY, WASHINGTON., US ISSN: 0022-2623 the whole document	1-9

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

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

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Patent document cited in search report		Publication date		Patent family member(s)	Publication date
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			JP	2001510479 T	31-07-2001
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			SK	103899 A3	16-05-2000
			TR	9901855 T2	21-04-2000
			US	6316432 B1	13-11-2001
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HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG,
MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR,
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- (54) Título: Uso de antiprogestinas para la profilaxis y el tratamiento de enfermedades dependientes de hormonas.
- (57) Resumen: Métodos y usos para prevenir o tratar enfermedades dependientes de hormonas, en particular cáncer de mama, en un mamífero mediante antiprogestinas, en particular la antiprogestina 11□-(4-acetilfenil)-17□-hidroxi-17□-(1,1,2,2,2-pentafluoroetil)-estra-4,9-dien-3-ona o un derivado o análogo de la misma aceptable para uso farmacéutico. La invención se relaciona además con composiciones farmacéuticas que comprenden dicha antiprogestina.

USO DE ANTIPROGESTINAS PARA LA PROFILAXIS Y EL TRATAMIENTO DE ENFERMEDADES DEPENDIENTES DE HORMONAS

Campo de la invención

La presente invención se relaciona con el uso de antiprogestinas para la profilaxis y el tratamiento de enfermedades dependientes de hormonas, en particular, cáncer de mama. La presente invención se relaciona además con composiciones farmacéuticas y formas de dosificación que comprenden antiprogestinas para la profilaxis y el tratamiento de enfermedades dependientes de hormonas, en particular cáncer de mama. Una antiprogestina particularmente preferida para usar en la invención es la antiprogestina 11β -(4-acetilfenil)- 17β -hidroxi- 17α -(1,1,2,2,2-pentafluoroetil)-estra-4,9-dien-3-ona, o un derivado o análogo de la misma aceptable para uso farmacéutico.

Antecedentes de la invención

La terapia endócrina representa un paradigma de tratamiento eficaz, mínimamente tóxico, paliativo para el cáncer de mama metastásico. Como tratamiento paliativo común para carcinomas mamarios no operables, así como coadyuvante en terapia después del tratamiento primario de carcinomas mamarios no operables, se usa el antiestrógeno tamoxifen. Sin embargo, el tamoxifen no puede curar el cáncer de mama. Así, para la terapia secundaria, se usan comúnmente progestinas o

inhibidores de aromatasa. En la ovariectomía de mujeres premenopáusicas, los análogos de tamoxifen y LHRH (hormona liberadora de hormona luteinizante) logran resultados comparables (H.T. Mouridson et al., *Eur. J. Cancer Clin. Oncol.*, 24, páginas 99-105, 1988).

Aunque el tamoxifen se usa ampliamente como coadyuvante en terapia para el cáncer de mama, su uso como agente quimiopreventivo es problemático, ya que se ha demostrado que el tratamiento resulta en un aumento en la incidencia de cánceres de endometrio (I.N.White, *Carcinogenesis*, 20(7): 1153-60, 1999).

Las antiprogestinas representan una clase relativamente nueva y prometedora de agentes terapéuticos que podrían tener un impacto significativo en el tratamiento de tumores dependientes de hormonas y otras enfermedades. Aunque las antiprogestinas fueron creadas originalmente para la terminación medicinal no quirúrgica del embarazo, algunas antiprogestinas han ganado una importancia considerable, p.ej., en la terapia en aquellos cánceres de mama que poseen receptores para progesterona (T. Maudelonde et al., en: J.G.M. Klijn et al., *Hormonal Manipulation of Cancer: Peptides, Growth Factors and New (Anti) Steroidal Agents*, Raven Press, Nueva York, 1987, páginas 55-59). Esta nueva estrategia en terapia endócrina se basa en la actividad antitumoral de las antiprogestinas en las líneas de células humanas de cáncer

de mama positivas para receptores *in vitro* y en varios tumores mamarios dependientes de hormonas de ratón y rata *in vivo*. En particular, el mecanismo antitumoral de las antiprogestinas onapristona y mifepristona (RU 486) ya ha sido investigado usando el modelo de tumor mamario MXT dependiente de hormonas, así como los modelos de tumores mamarios inducidos por DMBA y NMU en rata (M. R. Schneider et al., *Eur. J. Cancer Clin. Oncol.*, Volumen 25, N° 4, páginas 691-701, 1989; H. Michna et al., *Brest Cancer Research and Treatment* 14:275-288, 1989; H. Michna, *J. Steroid. Biochem.* Volumen 34, N° 1-6, páginas 447-453, 1989). Sin embargo, debido a la baja actividad y a los efectos colaterales adversos relacionados con, p.ej., la mifepristona, no pudo recomendarse este compuesto como agente individual en el manejo del cáncer de mama (D. Perrault et al., *J. Clin. Oncol.* 1996 Oct, 14(10), pág. 2709-2712).

Los compuestos de antiprogestina son adecuados para iniciar abortos y, así, para usarlos en el control de fertilidad postcoital, como anticonceptivos para mujeres (WO-A 93/23020, WO-A 93/21927) y, además, para el tratamiento de irregularidades hormonales, para iniciar la menstruación y para iniciar el trabajo de parto. Otras indicaciones son en el campo de la terapia de sustitución de hormonas (WO-A 94/18983), el tratamiento de afecciones relacionadas con la dismenorrea y el tratamiento de endometriosis (EP-A 0 266

303), así como miomas.

Los 17α -fluoroalquilesteroides que tienen una fuerte actividad antiprogestina, así como los métodos para producirlos, se describen en WO 98/34947.

Las antiprogestinas de la técnica previa evaluadas o usadas previamente debido a su actividad antitumoral muestran algunas desventajas.

Por ej., a pesar del hecho de que las antiprogestinas de la técnica previa mostraron actividad antigestagénica, estos compuestos no resultaron tratamientos adecuados para enfermedades dependientes de hormonas tales como el cáncer de mama. En particular, los compuestos de la técnica previa se asociaron con efectos colaterales, p.ej., la mifepristona muestra fuertes efectos colaterales antiglucocorticoides (véanse L.M. Kettel et al., *Fertil.Steril.* 1991 Sep, 56(3), páginas 402-407; X. Bertagna, *Psychoneuroendocrinology* 1997; 22 Suplemento 1, pág.51-55) y, además, mostró solamente una actividad moderada en ensayos clínicos (véase nuevamente D. Perrault et al., *J.Clin.Oncol.* 1996 Oct, 14(10), pág.2709-2712). Respecto de efectos colaterales de otras terapias basadas en hormonas, como ya se mencionó previamente, la administración de tamoxifen puede resultar en un aumento en la incidencia de cánceres de endometrio (I.N.White, *Carcinogenesis*, 20(7):1153-60, 1999).

Otro problema con las antiprogestinas de la técnica

previa era su biodisponibilidad pobre cuando se las administraba por vía oral. Así, generalmente tenían que administrarse en altas dosis, dando lugar a posibles efectos colaterales desfavorables. Más aún, la administración oral es deseable respecto de la conveniencia y el seguimiento por parte del paciente.

Además, existe aún una necesidad de compuestos que sean activos no solamente en el tratamiento, pero también en la profilaxis del cáncer de mama y otras enfermedades dependientes de hormonas. La incidencia incrementada de cáncer de endometrio asociada con el tamoxifen tiende a mostrar que este compuesto no es adecuado para el tratamiento de profilaxis de mujeres saludables, y no existen otros compuestos adecuados disponibles (véase L. Bergman et al., *The Lancet*, Vol. 356, Sept. 9, 2000; 881-887).

Objeto de la presente invención

Es un objeto de la presente invención prevenir o reducir las desventajas de los métodos de la técnica previa para prevenir o tratar enfermedades dependientes de hormonas, tales como el cáncer de mama. Se desea especialmente que el medio que se provee para prevenir y tratar enfermedades dependientes de hormonas, tales como cáncer de mama, mediante la administración de agentes altamente efectivos, sea superior a los métodos y agentes conocidos, incluyendo la ovariectomía. Así, se desea especialmente además proveer un tratamiento

de enfermedades dependientes de hormonas, tales como el cáncer de mama, que evite la severa cirugía altamente riesgosa asociada con la ovariectomía. Se desea además proveer un agente para usar de acuerdo con la invención que muestre menos efectos colaterales que los métodos previamente conocidos o sugeridos para tratar y prevenir enfermedades dependientes de hormonas tales como el cáncer de mama.

Es otro objeto de la presente invención proveer composiciones farmacéuticas que comprenden agentes antitumorales altamente efectivos para la profilaxis y el tratamiento del cáncer de mama y de otras enfermedades dependientes de hormonas.

Estos objetos se logran sorprendentemente mediante el uso de antiprogestinas de acuerdo con la presente invención y a través de composiciones farmacéuticas y formas de dosificación que comprenden tales antiprogestinas. Es particularmente preferida en este caso la antiprogestina 11β -(4-acetilfenil)- 17β -hidroxi- 17α -(1,1,2,2,2-pentafluoroetil)-estra-4,9-dien-3-ona o un derivado o análogo de la misma aceptable para uso farmacéutico.

Es otro objeto de la presente invención proveer antiprogestinas, tales como la antiprogestina 11β -(4-acetilfenil)- 17β -hidroxi- 17α -(1,1,2,2,2-pentafluoroetil)-estra-4,9-dien-3-ona o derivados o análogos de la misma aceptables para uso farmacéutico, que sean particularmente adecuadas para

administración oral.

Resumen de la invención

La presente invención se basa en la nueva e inesperada observación de que algunas antiprogestinas, en particular 11β -(4-acetilfenil)- 17β -hidroxi- 17α -(1,1,2,2,2-pentafluoroetil)-estra-4,9-dien-3-ona, o un derivado o análogo de la misma aceptable para uso farmacéutico, es excepcionalmente activa en la prevención y la reducción del crecimiento tumoral en los modelos de cáncer de mama inducidos por DMBA (7,12-dimetilbenzantraceno) y NMU (N-metilnitrosourea). De hecho, la antiprogestina 11β -(4-acetilfenil)- 17β -hidroxi- 17α -(1,1,2,2,2-pentafluoroetil)-estra-4,9-dien-3-ona (I) resultó ser distintivamente más potente que el tamoxifen y la ovariectomía en la prevención del desarrollo de cáncer de mama.

Así, la presente invención provee un método para la profilaxis y el tratamiento de cáncer de mama y otras enfermedades dependientes de hormonas en mamíferos, en particular humanos, que necesitan de tal tratamiento, que comprende administrar una cantidad efectiva para uso farmacéutico de una antiprogestina, en particular 11β -(4-acetilfenil)- 17β -hidroxi- 17α -(1,1,2,2,2-pentafluoroetil)-estra-4,9-dien-3-ona, o un derivado o análogo de la misma aceptable para uso farmacéutico, a un paciente.

La presente invención provee además composiciones farmacéuticas que comprenden una antiprogestina, en particular

11 β -(4-acetilfenil)-17 β -hidroxi-17 α -(1,1,2,2,2-pentafluoroetil)-estra-4,9-dien-3-ona, o un derivado o análogo de la misma aceptable para uso farmacéutico, en una cantidad suficiente para la profilaxis o el tratamiento de cáncer de mama u otras enfermedades dependientes de hormonas.

La antiprogestina preferida 11 β -(4-acetilfenil)-17 β -hidroxi-17 α -(1,1,2,2,2-pentafluoroetil)-estra-4,9-dien-3-ona se conocerá de aquí en adelante como "antiprogestina (I)".

Breve descripción de las figuras

La figura 1 muestra el efecto de prevención de desarrollo de tumores de la antiprogestina (I) en el carcinoma mamario de rata inducido por DMBA, en comparación con un control, tamoxifen y ovariectomía.

La figura 2 muestra los efectos inhibidores del crecimiento tumoral de la antiprogestina (I) en un estudio de respuesta a la dosis en el carcinoma mamario de rata inducido por DMBA, en comparación con un control, la antiprogestina onapristona, así como una ovariectomía. El estudio se realizó con dosis de 0,5, 2,0, 5,0 y 10,0 mg/kg s.c. de antiprogestina (I).

La figura 3 muestra el efecto de prevención del desarrollo tumoral de la antiprogestina (I) en el carcinoma mamario de rata inducido por NMU, en comparación con un control, los antiestrógenos raloxifen y tamoxifen, el inhibidor de la aromatasa letrozol, así como ovariectomía.

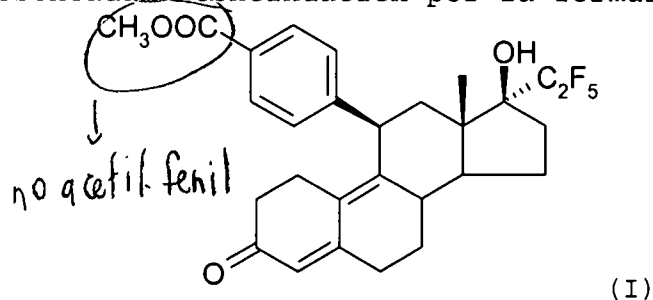
La figura 4 muestra el efecto inhibidor del crecimiento tumoral de dosis de 0,5 y 1,0 mg/kg de antiprogestina (I) en el carcinoma mamario de rata inducido por NMU, en comparación con un control, onapristona (5 mg/kg) y ovariectomía.

La figura 5 muestra el efecto inhibidor del crecimiento tumoral de la antiprogestina (I) en una dosis de 10 mg/kg s.c. en el modelo de xenoinjerto T47D humano en ratones SCID, en comparación con un control, así como ovariectomía.

La figura 6 muestra el efecto inhibidor del crecimiento tumoral de la antiprogestina (I) en una dosis de 10 mg/kg s.c. en el modelo de xenoinjerto MCF7 humano en ratones SCID, en comparación con un control, así como ovariectomía.

Descripción detallada de la invención

La antiprogestina (I) - 11 β -(4-acetilfenil)-17 β -hidroxi-17 α -(1,1,2,2,2-pentafluoroetil)-estra-4,9-dien-3-ona - está representada a continuación por la fórmula (I):



La antiprogestina (I) (o un derivado o análogo de la misma aceptable para uso farmacéutico) es un agente farmacéutico valioso que tiene una fuerte actividad antiprogestina. La antiprogestina (I) puede usarse de acuerdo con la

presente invención para la profilaxis y el tratamiento del cáncer de mama y otras enfermedades dependientes de hormonas.

El término "antiprogestina" en el contexto de la presente invención pretende comprender primariamente todos los compuestos que son capaces de inhibir competitivamente los receptores de progesterona. Sin embargo, debería abarcar también compuestos capaces de inhibir la biosíntesis de progestinas.

Los derivados o análogos aceptables para uso farmacéutico de la antiprogestina (I) en el contexto de la presente invención pueden incluir, p.ej., cualquiera de los compuestos de la invención que se describen en WO 98/34947.

El término "enfermedades dependientes de hormonas", en el contexto de la presente invención, puede incluir, sin limitaciones, cáncer de mama, cáncer de ovario, cáncer de endometrio, mieloma, infertilidad anovulatoria, meningioma, es decir, enfermedades que se originan o están influidas sustancialmente por la presencia de receptores de hormonas y/o vías dependientes de hormonas.

Respecto de la superioridad de la presente invención sobre la técnica previa, es especialmente favorable que, p.ej., con la antiprogestina (I), usada de acuerdo con la presente invención, los efectos colaterales endócrinos adicionales, tales como, p.ej., la actividad de los andrógenos,

los estrógenos o los antiglucocorticoides es solamente muy débil, si llega a estar presente. Debido a la alta biodisponibilidad de la antiprogestina (I), puede administrársela por vía oral, tornando así el tratamiento para un paciente que lo necesita tan conveniente como sea posible. Como consecuencia favorable adicional, la antiprogestina (I) es bien tolerada y puede administrarse en dosis relativamente bajas en comparación con los tratamientos establecidos, reduciendo así los efectos colaterales indeseados, tales como un aumento en la incidencia de cánceres de endometrio con la administración de tamoxifen (véanse I.N. White, *Carcinogenesis*, 20(7):1153-60, 1999; L. Bergman et al., *The Lancet*, Vol. 356, Sept. 9, 2000, 881-887), así como los efectos antiglucocorticoides y algunos efectos colaterales tóxicos relacionadas con la administración de mifepristona (véanse D. Perrault et al., *J. Clin. Oncol.* 1996 Oct, 14(10), páginas 2709-2712; L.M. Kettel et al., *Fertil. Steril.* 1991 Sep, 56(3), páginas 402-407; X. Bertagna, *Psychoneuroendocrinology* 1997, 22 Suplemento 1; pág. 51-55).

Otra ventaja de la presente invención sobre la técnica previa es la provisión de un método efectivo para la profilaxis de enfermedades dependientes de hormonas tales como el cáncer de mama, de modo tal que los pacientes con alto riesgo de desarrollar o desarrollar nuevamente enfermedades dependientes de hormonas pueden ser tratados para evitar la

incidencia de tales enfermedades.

En un primer aspecto, la presente invención se relaciona con un método para la profilaxis o el tratamiento de cáncer de mama y otras enfermedades dependientes de hormonas, que comprende administrar al menos una antiprogestina, preferiblemente antiprogestina (I) o un derivado o análogo de la misma aceptable para uso farmacéutico a un mamífero, preferiblemente a un humano, que necesita de tal profilaxis o tratamiento.

En otro aspecto, la presente invención se relaciona con el uso de antiprogestinas como se las describió previamente, preferiblemente antiprogestina (I) o un derivado o análogo de la misma aceptable para uso farmacéutico, para la fabricación de un medicamento, en particular para la profilaxis o el tratamiento de cáncer de mama u otras enfermedades dependientes de hormonas.

En otro aspecto, la presente invención se relaciona con composiciones farmacéuticas que comprenden al menos una antiprogestina como se la definió previamente, preferiblemente antiprogestina (I) o un derivado o análogo de la misma aceptable para uso farmacéutico. Opcionalmente, la antiprogestina (I) puede combinarse con otros agentes farmacológicamente activos. P.ej., la antiprogestina puede combinarse también con un agente citotóxico para un tratamiento mediante la unión a un receptor de hormonas.

La fabricación de medicamentos puede realizarse de acuerdo con métodos conocidos en la técnica. Pueden usarse coadyuvantes, así como otros vehículos o diluyentes adecuados. Los vehículos o coadyuvantes adecuados pueden ser como se los recomienda para campos farmacéuticos, cosméticos y relacionados en: *Ullmann's Encyclopedia of Technical Chemistry*, Volumen 4, (1953), páginas 1-39; *Journal of Pharmaceutical Sciences*, Volumen 52 (1963), pág. 918ff; H.v. Czetsch-Lindenwald, "Hilfsstoffe für Pharmazie und angrenzende Gebiete"; *Pharm. Ind.* 2, 1961, p. 72ff; Dr. H.P. Fiedler, *Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete*, Cantor KG, Aulendorf in Württemberg, 1971.

Las antiprogestinas adecuadas para los propósitos de la presente invención, preferiblemente antiprogestina (I) o un derivado o análogo de la misma aceptable para uso farmacéutico, pueden incorporarse en composiciones farmacéuticas de acuerdo con métodos conocidos para preparar composiciones medicinales para aplicación oral o parenteral, p.ej., intraperitoneal, intramuscular, subcutánea o percutánea. Pueden implantarse también en el tejido. Los implantes pueden comprender materiales inertes, p.ej., polímeros biológicamente degradables o siliconas sintéticas tales como, p.ej., goma de silicona.

Pueden administrarse bajo la forma de tabletas, píldoras, grageas, cápsulas de gel, gránulos, supositorios, im-

plantes, soluciones, suspensiones o emulsiones acuosas u oleosas estériles inyectables, ungüentos, cremas, geles o mediante sistemas intravaginales (p.ej., anillos vaginales) o intrauterinos (p.ej., diafragmas, rizos).

Para la preparación de un medicamento para administración oral, las antiprogestinas adecuadas para los propósitos de la presente invención que se definieron previamente pueden mezclarse con coadyuvantes o vehículos comúnmente conocidos tales como p.ej., goma arábica, talco, almidón, azúcares tales como, p.ej., manitosa, metil celulosa, lactosa, gelatina, agentes activos en superficie, estearato de magnesio, excipientes acuosos o no acuosos, derivados de parafina, agentes reticulantes, dispersantes, emulsificadores, lubricantes, agentes conservantes y agentes saborizantes (p.ej., aceites etéreos). En una composición farmacéutica, la antiprogestina puede dispersarse en una nanopartícula, p.ej., una composición nanoparticulada.

Con el fin de mejorar la biodisponibilidad del agente activo, las antiprogestinas adecuadas para los propósitos de la presente invención que se definieron previamente pueden formularse también como clatratos de ciclodextrinas haciéndolas reaccionar con α -, β - o γ -ciclodextrinas o derivados de las mismas de acuerdo con el método que se describe en PCT/EP95/02656.

Para administración parenteral, las antiprogestinas

adecuadas para los propósitos de la presente invención que se definieron previamente pueden disolverse o suspenderse en un diluyente aceptable para el uso fisiológico tal como, p.ej., aceites con o sin solubilizadores, agentes activos en superficie, dispersantes o emulsificadores. Como aceites, p.ej. y sin limitación, puede usarse aceite de oliva, aceite de maní, aceite de semilla de algodón, aceite de soja, aceite de castor y aceite de sésamo.

La cantidad a administrar (es decir, una "cantidad efectiva para uso farmacéutico") varía dentro de un amplio rango y depende de la condición a tratar y del modo de administración. Puede cubrir cualquier cantidad suficiente para el tratamiento que se pretende. La determinación de una "cantidad efectiva para uso farmacéutico" está dentro del conocimiento de aquél entrenado en la técnica.

Una dosis unitaria puede representar entre aproximadamente 0,1 y 100 mg de agentes activos. Para una administración a humanos, la dosis diaria de agente activo es entre aproximadamente 0,1 y 400 mg, preferiblemente entre 10 y 100 mg, más preferiblemente de 50 mg.

Las composiciones farmacéuticas de acuerdo con la presente invención pueden también administrarse vía una inyección de depósito, una preparación de implante o un IUD (dispositivo intrauterino), opcionalmente para la liberación sostenida de los agentes.

El modo preferido de administración es administración oral. Las antiprogestinas que se usan de acuerdo con la invención, y en particular, antiprogestina (I) o un derivado o análogo de la misma aceptable para uso farmacéutico, son particularmente adecuadas para administración oral.

De acuerdo con todos los aspectos de la presente invención, es también posible combinar al menos una antiprogestina como se definió previamente, en particular antiprogestina (I) o un derivado o análogo de la misma aceptable para uso farmacéutico, con al menos un antiestrógeno, ya que muchas enfermedades dependientes de hormonas, en particular cáncer de mama, muestran no solamente receptores de progesterona sino también receptores de estrógeno. El antiestrógeno puede administrarse en forma simultánea o consecutiva respecto de la antiprogestina (I) o un derivado o análogo de la misma aceptable para uso farmacéutico. La cantidad de antiprogestina y antiestrógeno puede ser igual o un componente puede ser más predominante que el otro, tal como en una relación antiprogestina: antiestrógeno ratio de 1:50 a 50:1, preferiblemente de 1:30 a 30:1, y más preferiblemente de 1:15 a 15:1.

Los ejemplos de antiestrógenos adecuados para un uso de acuerdo con la invención son antiestrógenos no esteroideos tales como tamoxifen y nafoxidina, así como raloxifen, faslodex y EM800. Los ejemplos de antiestrógenos esteroideos incluyen aquellos descritos en EP 0 348 341 A y aquellos

descriptos en WO 98/07740, en particular, 11 β -flouro-7 α -{5-[N-metil-N-3-(4,4,5,5,5-pentafluoropentiltio-propilamino)-pentil]-estra-1,3,5(10)-trien-3,17 β -diol, o aquellos descritos en WO 99/33855, en particular 11 β -flouro-7 α -{5-[metil-(7,7,8,8,9,9,10,10,10-nonafluoro-decil)-amino]-pentil]-estra-1,3,5(10)-trien-3,17 β -diol, o los derivados o análogos de los mismos aceptables para uso farmacéutico. Pueden usarse también como antiestrógenos inhibidores de aromatasas que tienen un efecto antiestrogénico, tales como aquellos que se describen en las páginas 7 a 8 de EP 0 495 825 B1.

La invención se ilustra adicionalmente en los ejemplos. Los siguientes ejemplos no deben interpretarse como una limitación.

Ejemplos

Ejemplo 1:

Modelo de cáncer de mama inducido por DMBA en rata (experimento de prevención)

Materiales y Métodos:

Se usaron ratas hembras inmaduras Sprague-Dawley (49 - 51 días de edad; 10 animales/grupo) en este estudio. Se administró el carcinógeno 7,12-dimetilbenz[a]antraceno (DMBA) como una única administración oral (10 mg). Se comenzó el tratamiento 20 días después como sigue: 1) solvente control, 2) ovariectomía al inicio del tratamiento, 3) tamoxifen, 1 mg/kg s.c., 4) antiprogestina (I), 3 mg/kg, s.c., 6 dí-

as/semana. Las ratas se examinaron cada semana por palpado de tumores de mama. Como parámetro de inhibición de crecimiento, se usó el cambio en el área tumoral (en % respecto del tamaño inicial del tumor) determinado por mediciones semanales de calibre. Para una descripción y evaluación adicional de los modelos de prevención de DMBA y NMU, véase R.G. Metha, *European Journal of Cancer* 36 (2000), páginas 1275-1282.

Resultados:

En el grupo control, todas las ratas desarrollaron tumores mamarios dentro de las 10 semanas posteriores al inicio del tratamiento (incidencia: 100%) y se observó un crecimiento progresivo del tumor. El tratamiento profiláctico con la antiprogestina (I) previno el desarrollo de tumores por completo durante 12 semanas, y al final del experimento, después de 22 semanas, se detectó un tumor solamente en una rata (incidencia: 10%). Después de la ovariectomía al final del experimento, 40% de las ratas habían desarrollado tumores. En comparación, el tratamiento con el antiestrógeno tamoxifen redujo la incidencia de tumores solamente al 60% (véase la fig. 1)

Conclusión:

En el modelo de tumor mamario inducido por DMBA en rata, la antiprogestina (I) suprimió completamente el desarrollo de tumores en animales intactos por más de 12 semanas

después del inicio del tratamiento. La figura 1 muestra claramente la superioridad en la actividad de la antiprogestina (I) sobre el reactivo convencional contra el cáncer de mama, tamoxifen, y aún la terapia común de privación de estrógeno (ovariectomía), respecto del tratamiento profiláctico. La antiprogestina (I) es así superior a la terapia común establecida para prevenir el cáncer de mama en mujeres con alto riesgo de desarrollar la enfermedad (terapia profiláctica con tamoxifen).

Estos y los siguientes resultados indican que el uso de antiprogestina (I) para la profilaxis y el tratamiento del cáncer de mama es superior a los tratamientos comunes establecidos.

Ejemplo 2:

Modelo de cáncer de mama inducido por DMBA en rata (experimento de terapia/estudio de respuesta a la dosis)

Materiales y Métodos:

Se usaron ratas hembras inmaduras Sprague-Dawley (49 - 51 días de edad; 10 animales/grupo) en este estudio. Se indujeron tumores mamarios a través de una única administración oral de 10 mg de 7,12-dimetilbenz[a]antraceno (DMBA, Serva/Heidelberg). Las ratas con al menos un tumor establecido con un tamaño de más de 150 mm² se trataron por 4 semanas con: 1) solvente control, 2) ovariectomía al inicio del tratamiento, 3) antiprogestina (I), 0,5 mg/kg s.c., 4) anti-

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progestina (I), 2 mg/kg s.c., 5) antiprogestina (I), 5 mg/kg s.c., 6) antiprogestina (I), 10 mg/kg s.c., y 7) onapristona, 5 mg/kg, s.c., diariamente. Como parámetro de inhibición de crecimiento, se usó el cambio en el área tumoral (en % respecto del tamaño inicial del tumor) determinado por mediciones semanales de calibre. Para el análisis estadístico de las diferencias entre grupos de valores medios, se usó la prueba de Kruskal-Wallis.

Resultados:

En los animales control intactos, se observó un crecimiento progresivo de los tumores, mientras que la ovariectomía causó una regresión considerable de los tumores en 90% de los animales. El tratamiento con antiprogestina (I) a dosis de 2 mg/kg o superiores resultó en una inhibición significativa del crecimiento tumoral en comparación con el control (véase la fig. 2). Existió una relación clara de dosis-respuesta. Mientras que el tratamiento con 0,5 mg/kg de antiprogestina (I) no evitó significativamente el crecimiento del tumor, a 2 mg/kg se observó una inhibición máxima del crecimiento tumoral. En este grupo, se observó una regresión completa del tumor en 50% de las ratas. El efecto de la mayor dosis de antiprogestina (I) evaluada en este experimento (10 mg/kg), fue comparable a aquél de 2 mg/kg. La onapristona (5 mg/kg, s.c.) fue notablemente menos efectiva que la antiprogestina (I) a dosis comparables.

Conclusión:

En el modelo de tumor mamario inducido por DMBA en rata, la antiprogestina (I) suprimió completamente el crecimiento tumoral en animales intactos. Se halló que la dosis de 2 mg/kg de antiprogestina (I) tiene un efecto máximo sobre el crecimiento tumoral. La antiprogestina (I) fue notablemente superior a la onapristona.

Ejemplo 3:

Modelo de cáncer de mama inducido por NMU en rata (experimento de prevención)

Materiales y Métodos:

Se indujeron tumores mediante una única inyección intravenosa de NMU (nitrosometilurea, 50 mg/kg) en ratas hembra Sprague-Dawley (obtenidas de Tierzucht Schönwalde, edad: 50-55 días). Comenzando 10 después, las ratas con al menos un tumor establecido se trataron por 4 semanas con: 1) solvente control, 2) ovariectomía al inicio del tratamiento, 3) antiprogestina (I), 1,0 mg/kg/día, 4) antiprogestina (I), 0,5 mg/kg/día y 5) onapristona, 5 mg/kg/día. Como parámetro de inhibición del crecimiento, se usó el cambio en el área tumoral (en % del tamaño inicial del tumor). Para una descripción y una evaluación adicional del modelo de prevención DMBA y NMU, véase R.G. Metha, *European Journal of Cancer* 36 (2000), páginas 1275-1282.

Resultados:

En el grupo control, todas las ratas desarrollaron tumores mamarios a los 10 días después del inicio del tratamiento (incidencia: 100%; véase la fig. 3) y se observó un crecimiento tumoral progresivo. El tratamiento profiláctico con la antiprogestina (I) previno el desarrollo tumoral completamente por 12 semanas, y al final experimento, después de 27 semanas, se detectó un tumor en solamente una rata (incidencia: 10%). En comparación, en el tratamiento con los otros antiestrógenos o el inhibidor de aromatasa letrozol, la incidencia de tumores se redujo solamente un 20 - 60%. Después de la ovariectomía al final del experimento, 20% de las ratas habían desarrollado tumores.

Conclusión:

En el modelo de tumor mamario inducido por MNU en rata, la antiprogestina (I) suprimió completamente el desarrollo de tumores en animales intactos por más de 12 semanas después del inicio del tratamiento. El efecto del tratamiento profiláctico con antiprogestina (I) fue superior a aquél de los antiestrógenos convencionales para la terapia de cáncer de mama (es decir, raloxifen, tamoxifen) y el inhibidor de la aromatas letrozol y la terapia común de privación de estrógeno (ovariectomía) en lo que respecta a la incidencia y el crecimiento tumoral.

Como en el modelo de tumor inducido por DMBA (véase el Ejemplo 1), estos resultados indican que la antiprogestina

(I) previene efectivamente el desarrollo de tumores de mama de una manera que es superior al tratamiento profiláctico normal, p.ej., con tamoxifen.

Ejemplo 4:

Modelo de cáncer de mama inducido por NMU en rata (experimento de terapia)

Materiales y Métodos:

Se indujeron tumores mediante una única inyección intravenosa de NMU (nitrosometilurea, 50 mg/kg) en ratas hembra Sprague-Dawley (obtenidas de Tierzucht Schönwalde, edad: 50-55 días). Comenzando 10 después, las ratas con al menos un tumor establecido se trataron por 4 semanas con: 1) solvente control, 2) ovariectomía al inicio del tratamiento, 3) anti-progestina (I), 1,0 mg/kg/día, 4) antiproggestina (I), 0,5 mg/kg/día y 5) onapristona, 5 mg/kg/día. Como parámetro de inhibición del crecimiento, se usó el cambio en el área tumoral (en % del tamaño inicial del tumor). Para el análisis estadístico de las diferencias entre grupos de los valores medios, se usó la prueba de Kruskal-Wallis.

Resultados:

En los animales control intactos, se observó un crecimiento progresivo de los tumores, mientras que la ovariectomía causó una inhibición completa de los tumores. El tratamiento con antiproggestina (I) a dosis de 0,5 ó 1,0 mg/kg resultó en una inhibición significativa del crecimiento del

tumor en comparación con el control (véase la fig. 2). La onapristona (5 mg/kg) fue notablemente menos efectiva que la antiprogestina (I) a la dosis mucho menor de 0,5 mg/kg.

Conclusiones:

En el modelo de tumor mamario inducido por MNU en rata, la antiprogestina (I) suprime completamente el crecimiento tumoral en animales intactos. Se halló que una dosis de 1,0 mg/kg y aún una dosis de 0,5 mg/kg de antiprogestina (I) tiene un efecto significativo sobre el crecimiento tumoral. Así, la antiprogestina (I) fue superior a antiprogestinas conocidas como la onapristona.

Ejemplo 5:

Xenoinjerto humano T47D (experimento de terapia)

Materiales y Métodos:

Se suplieron ratones hembra Fox Chase SCID (M&B) con pellets de estradiol (Innovative Research of America). Las células T47D de cáncer de mama, obtenidas de cultivos celulares y suspendidas en matrigel, se implantaron por vía s.c. en la región inguinal del ratón. El tratamiento comenzó cuando los tumores tenían aproximadamente 25 mm² de tamaño. Se continuó el tratamiento hasta que progresaran los tumores. Los grupos experimentales fueron: 1) control (vehículo), 2) ovariectomía, 3) antiprogestina (I), 10 mg/kg s.c. Se determinó el área tumoral por mediciones de calibre. Para el análisis estadístico de las diferencias entre grupos de

los valores medios, se usó la prueba de Kruskal-Wallis.

Resultados:

En el modelo T47D de cáncer de mama, la ovariectomía resultó en una inhibición considerable del crecimiento de los tumores, en comparación con el crecimiento rápido del control. La figura 5 muestra que la aplicación s.c. de 10 mg/kg de antiprogesterina (I) causa inhibición sobre el crecimiento tumoral. El efecto de la antiprogesterina (I) es casi comparable con el efecto de la terapia convencional de privación de estrógeno (ovariectomía).

Conclusión:

El efecto de la antiprogesterina (I) en la inhibición del crecimiento tumoral y, así, en la inhibición del crecimiento del cáncer de mama T47D xenoinjertado en ratones Fox Chase SCID es comparable al efecto de la terapia común de privación de estrógeno (ovariectomía), que se considera como el método más efectivo para inhibir el crecimiento de cáncer de mama en este modelo.

Ejemplo 6:

Xenoinjerto humano MCF7 (experimento de terapia)

Materiales y Métodos:

Se suplieron ratones hembra Fox Chase SCID (M&B) con pellets de estradiol (Innovative Research of America). Las células T47D de cáncer de mama, obtenidas de cultivos celulares y suspendidas en matrigel, se implantaron por vía s.c.

en la región inguinal del ratón. El tratamiento comenzó cuando los tumores tenían aproximadamente 25 mm² de tamaño. Se continuó el tratamiento hasta que progresaran los tumores. Los grupos experimentales fueron: 1) control (vehículo), 2) ovariectomía, 3) antiprogesterina (I), 10 mg/kg s.c. Se determinó el área tumoral por mediciones de calibre. Para el análisis estadístico de las diferencias entre grupos de los valores medios, se usó la prueba de Kruskal-Wallis.

Resultados:

En el modelo MCF7 de cáncer de mama, la ovariectomía resultó en una inhibición considerable del crecimiento de los tumores, en comparación con el crecimiento rápido del control. La figura 6 muestra que la aplicación de 10 mg/kg de antiprogesterina (I) causó también una inhibición del crecimiento tumoral, casi comparable con el efecto de la terapia convencional de privación de estrógeno (ovariectomía).

Conclusión:

El efecto de la antiprogesterina (I) en la inhibición del crecimiento del cáncer de mama humano MCF7 xenoinjertado en ratones SCID Fox Chase es comparable al efecto de la terapia común de privación de estrógeno (ovariectomía), que se considera como el método más efectivo para inhibir el crecimiento de cáncer de mama en este modelo.

REIVINDICACIONES

1. Uso de la antiprogestina 11β -(4-acetilfenil)- 17β -hidroxi- 17α -(1,1,2,2,2-pentafluoroetil)-estra-4,9-dien-3-ona, o un derivado o análogo de la misma aceptable para uso farmacéutico, para la fabricación de un medicamento para la profilaxis o el tratamiento de una enfermedad dependiente de hormonas en un mamífero.

2. Un uso de acuerdo con la reivindicación 1 donde la enfermedad es cáncer de mama.

3. Un uso de acuerdo con las reivindicaciones 1 ó 2 donde el mamífero es un ser humano.

4. Un uso de acuerdo con cualquiera de las reivindicaciones precedentes donde el medicamento se administra por vía oral.

5. Un uso de acuerdo con cualquiera de las reivindicaciones precedentes donde la antiprogestina 11β -(4-acetilfenil)- 17β -hidroxi- 17α -(1,1,2,2,2-pentafluoroetil)-estra-4,9-dien-3-ona se administra en una unidad de dosificación de 50 mg.

6. Una composición farmacéutica que comprende la antiprogestina 11β -(4-acetilfenil)- 17β -hidroxi- 17α -(1,1,2,2,2-pentafluoroetil)-estra-4,9-dien-3-ona, o un derivado o análogo de la misma aceptable para uso farmacéutico, en una cantidad suficiente para la profilaxis o el tratamiento de

una enfermedad dependiente de hormonas en un mamífero.

7. Una composición farmacéutica de acuerdo con la reivindicación 6 donde la enfermedad es cáncer de mama.

8. Una composición farmacéutica de acuerdo con las reivindicaciones 6 ó 7 donde el mamífero es un ser humano.

9. Una composición farmacéutica de acuerdo con cualquiera de las reivindicaciones 6 a 8 que comprende además un antiestrógeno.

5 **USE OF ANTIPROGESTINS FOR PROPHYLAXIS AND
TREATMENT OF HORMONE-DEPENDENT DISEASES**

10 Field of the Invention

The present invention relates to the use of antiprogestins for the prophylaxis and treatment of hormone-dependent diseases, in particular breast cancer. The present invention further relates to pharmaceutical compositions and dosage forms comprising antiprogestins for the prophylaxis and treatment of hormone-dependent diseases, in particular breast cancer.

15 A particularly preferred antiprogestin for use in the invention is the antiprogestin 11β -(4-acetylphenyl)- 17β -hydroxy- 17α -(1,1,2,2,2-pentafluoroethyl)-estra-4,9-dien-3-one or a pharmaceutically acceptable derivative or analogue thereof.

20 Background of the Invention

Endocrine therapy represents a mainstay of effective, minimally toxic, palliative treatment for metastatic breast cancer. As a standard palliative treatment of non-operable mammary carcinomas as well as for adjuvant therapy after primary treatment of mammary carcinomas predominantly the antiestrogen tamoxifen is used. However, tamoxifen cannot
25 cure breast cancer. Thus, for secondary therapy progestins or aromatase inhibitors are commonly used. In premenopausal women ovariectomy, tamoxifen and LHRH (luteinizing hormone releasing hormone) analogs achieve comparable results (H.T. Mouridson et al., *Eur. J. Cancer Clin. Oncol.*, 24, pp. 99-105, 1988).

30 Although tamoxifen is widely used for adjuvant therapy of breast cancer, its use as a chemopreventive agent is problematic, because it has been shown that the treatment

results in an increase in the incidence of endometrial cancers (I.N. White, *Carcinogenesis*, 20(7):1153-60, 1999).

Antiprogestins represent a relatively new and promising class of therapeutic agents that
5 could have significant impact on breast cancer treatment. Although antiprogestins were
originally created with regard to medicinal non-surgical termination of pregnancy (EP 129
499), certain antiprogestins have recently gained importance in the endocrine therapy of
those breast cancers involving receptors for progesterone (T. Maudelonde et al., in: J.G.M.
Klijn et al., *Hormonal Manipulation of Cancer: Peptides, Growth Factors and New (Anti)*
10 *Steroidal Agents*, Raven Press, New York, 1987, pp. 55-59). This new strategy in
endocrine therapy is based on the antitumor activity of antiprogestins in progesterone
receptor-positive human breast cancer cell lines *in vitro* and in several hormone-dependent
mammary tumors of the mouse and rat *in vivo*. In particular, the antitumor mechanism of
the antiprogestins onapristone and mifepristone (RU 486) was investigated using the
15 hormone-dependent MXT mammary tumor model of the mouse as well as the DMBA-
and the NMU-induced mammary tumor models of the rat (M. R. Schneider et al., *Eur. J.*
Cancer Clin. Oncol., Vol. 25, No. 4, pp. 691-701, 1989; H. Michna et al., *Breast Cancer*
Research and Treatment 14:275-288, 1989; H. Michna, *J. Steroid. Biochem.* Vol. 34, Nos
1-6, pp. 447-453, 1989). However, due to low activity and adverse side effects involved
20 with e.g. mifepristone this compound could not be recommended as a single agent in the
management of breast cancer (D. Perrault et al., *J. Clin. Oncol.* 1996 Oct, 14(10),
pp.2709-2712).

Antiprogesterin compounds are suitable for initiating abortions and thus for use in postcoital
25 fertility control, as contraceptives for women (WO-A 93/23020, WO-A 93/21927) and
further for the treatment of hormone irregularities, for initiating menstruation and for
initiating labor. Further indications are in the field of hormone substitution therapy (WO-
A 94/18983), the treatment of afflictions related to dysmenorrhea and the treatment of
endometriosis (EP-A 0 266 303) as well as myomas.
30 17 α -fluoroalkylsteroids having strong antiprogesterin activity as well as methods for
producing them are described in WO 98/34947.

Antiprogestins of the prior art tested or used previously due to their antitumor activity frequently exhibited certain disadvantages.

- 5 For example, despite the fact that prior art antiprogestins exhibited antigestagenic activity, these compounds were not suitable treatments for hormone-dependent diseases such as breast cancer. In particular, prior art compounds were associated with side effects, e.g. mifepristone exhibits strong antiglucocorticoid side effects (cf. L.M. Kettel et al., *Fertil. Steril.* 1991 Sep, 56(3), pp: 402-407; X. Bertagna, *Psychoneuroendocrinology* 1997; 22 Suppl. 1; pp. 51-55) and besides it showed only moderate activity in clinical trials (see again D. Perrault et al., *J. Clin. Oncol.* 1996 Oct, 14(10), pp.2709-2712). Regarding side effects of other hormone-based therapies, as already mentioned above, tamoxifen administration can result in an increase in the incidence of endometrial cancers (I.N. White, *Carcinogenesis*, 20(7):1153-60, 1999).

15

Another problem with prior art antiprogestins was poor bioavailability when administered orally. Thus, they generally had to be administered in high doses, giving rise to possible unfavorable side effects. Moreover, oral administration is desirable with respect to patient convenience and compliance.

20

- Furthermore, there is still a need for compounds that are active not only in the treatment, but also in the prophylaxis of breast cancer and other hormone-dependent diseases. The increased incidence of endometrial cancer associated with tamoxifen tends to show that this compound is unsuitable for prophylaxis treatment of healthy women, and no other suitable compounds are available (cf. L. Bergman et al., *The Lancet*, Vol. 356, Sept. 9, 2000; 881-887).

25

30 Object of the Present Invention

It is an object of the present invention to prevent or reduce the disadvantages of the prior art methods for preventing or treating hormone-dependent diseases, such as breast cancer. It is especially desired that a means of preventing and treating hormone-dependent diseases, such as breast cancer, via the administration of highly effective agents is provided that is superior to known methods and agents, including ovariectomy. Thus it is further especially desired to provide a treatment of hormone-dependent diseases, such as breast cancer, that prevents serious and risk-laden surgery involved with ovariectomy. It is further desired to provide an agent for use according to the invention exhibiting less side effects than previously known or suggested methods for treating and preventing hormone-dependent diseases such as breast cancer.

It is a further object of the present invention to provide pharmaceutical compositions comprising highly effective antitumor agents for the prophylaxis and treatment of breast cancer and other hormone-dependent diseases.

15

These objects are surprisingly achieved by the use of antiprogestins according to the present invention and by pharmaceutical compositions and dosage forms comprising such antiprogestins. Particularly preferred in this regard is the antiprogestin 11β -(4-acetylphenyl)- 17β -hydroxy- 17α -(1,1,2,2,2-pentafluoroethyl)-estra-4,9-dien-3-one or a pharmaceutically acceptable derivative or analogue thereof.

20

It is a further object of the present invention to provide antiprogestins, such as the antiprogestin 11β -(4-acetylphenyl)- 17β -hydroxy- 17α -(1,1,2,2,2-pentafluoroethyl)-estra-4,9-dien-3-one or pharmaceutically acceptable derivatives or analogues thereof, that are particularly suitable for oral administration.

25

Summary of the Invention

The present invention is based on the novel and unexpected observation that certain antiprogestins, in particular 11β -(4-acetylphenyl)- 17β -hydroxy- 17α -(1,1,2,2,2-pentafluoroethyl)-estra-4,9-dien-3-one or a pharmaceutically acceptable derivative or analogue thereof, are exceptionally active in the prevention and reduction of tumor growth

30

in DMBA (7,12-dimethylbenzanthracene)- and NMU (N-methylnitrosourea)-induced breast cancer models. In fact, the antiprogesterin 11 β -(4-acetylphenyl)-17 β -hydroxy-17 α -(1,1,2,2,2-pentafluoroethyl)-estra-4,9-dien-3-one (I) turned out to be distinctly more potent than tamoxifen and ovariectomy in the prevention of breast cancer development.

5

Thus, the present invention provides a method for prophylaxis and treatment of breast cancer and other hormone-dependent diseases in mammals, in particular humans, in need of such treatment, said method comprising administering a pharmaceutically effective amount of an antiprogesterin, in particular 11 β -(4-acetylphenyl)-17 β -hydroxy-17 α -(1,1,2,2,2-pentafluoroethyl)-estra-4,9-dien-3-one, or a pharmaceutically acceptable derivative thereof or analogue thereof, to a patient.

10

The present invention further provides pharmaceutical compositions comprising an antiprogesterin, in particular 11 β -(4-acetylphenyl)-17 β -hydroxy-17 α -(1,1,2,2,2-pentafluoroethyl)-estra-4,9-dien-3-one or a pharmaceutically acceptable derivative or analogue thereof, in an amount sufficient for the prophylaxis or treatment of breast cancer or other hormone-dependent diseases.

15

20

The preferred antiprogesterin 11 β -(4-acetylphenyl)-17 β -hydroxy-17 α -(1,1,2,2,2-pentafluoroethyl)-estra-4,9-dien-3-one will hereinafter be referred to as "antiprogesterin (I)".

Brief Description of the Figures

25

Figure 1 shows the tumor development prevention effect of antiprogesterin (I) in the DMBA-induced mammary carcinoma of the rat, compared with a control, tamoxifen and ovariectomy.

30

Figure 2 shows the tumor growth inhibiting effects of antiprogesterin (I) in a dose-response study in the DMBA-induced mammary carcinoma of the rat, compared with a control, the antiprogesterin onapristone as well as ovariectomy. The study was performed with 0.5, 2.0, 5.0 and 10.0 mg/kg s.c. doses of antiprogesterin (I).

Figure 3 shows the tumor development prevention effect of antiprogesterin (I) in the NMU-induced mammary carcinoma of the rat, compared with a control, the antiestrogens raloxifen and tamoxifen, the aromatase inhibitor letrozol as well as ovariectomy.

5

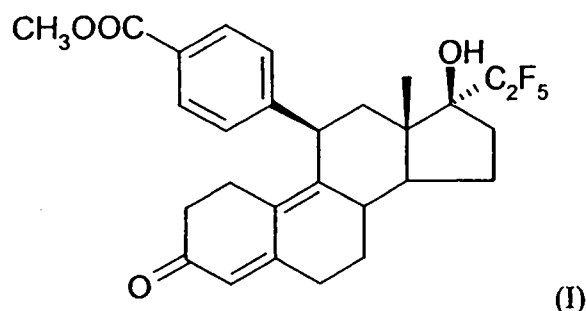
Figure 4 shows the tumor growth inhibiting effect of 0.5 and 1.0 mg/kg doses of antiprogesterin (I) in the NMU-induced mammary carcinoma of the rat, compared with a control, onapristone (5 mg/kg) and ovariectomy.

10 Figure 5 shows the tumor growth inhibiting effect of antiprogesterin (I) in a 10 mg/kg s.c. dose in the T47D human xenograft in scid mice, compared to a control as well as ovariectomy.

15 Figure 6 shows the tumor growth inhibiting effect of antiprogesterin (I) in a 10 mg/kg s.c. dose in the MCF7 human xenograft in scid mice, compared to a control as well as ovariectomy.

Detailed Description of the Invention

20 Antiprogesterin (I) — 11 β -(4-acetylphenyl)-17 β -hydroxy-17 α -(1,1,2,2,2-pentafluoroethyl)-estra-4,9-dien-3-one — is represented below by formula (I):



25 Antiprogesterin (I) (or a pharmaceutically acceptable derivative or analogue thereof having comparable activity) is a valuable pharmaceutical agent having strong antiprogesterin activity. Antiprogesterin (I), as well as further antiprogesterins, can be used according to the

present invention for the prophylaxis and treatment of breast cancer and other hormone-dependent diseases.

5 The term "antiprogestin" in the context of the present invention is intended to primarily comprise all compounds being capable of competitively inhibiting progesterone receptors. However, it should also encompass compounds capable of inhibiting the biosynthesis of progestins.

40 A pharmaceutically acceptable derivative or analogue of antiprogestin (I) in the context of the present invention may include, for example, any one of the inventive compounds disclosed in WO 98/34947.

15 The term "hormone-dependent diseases" in the context of the present invention may include, but is not limited to, breast cancer, ovarian cancer, endometrial cancer, myeloma, anovulatory infertility, meningoma, i.e. diseases which substantially originate or are influenced by the presence of hormone receptors and/or hormone-dependent pathways.

20 As regards the superiority of the present invention over the prior art, it is especially favorable that, e.g., in antiprogestin (I) used according to the present invention further endocrine side effects, such as e.g. androgen, estrogen or antiglucocorticoid activity are only very weak, if present at all. Due to the high bioavailability of antiprogestin (I) it can be administered orally, thus rendering the treatment for a patient in need thereof as convenient as possible. As a further favorable consequence, antiprogestin (I) is well tolerated and can be administered in relatively low doses compared to established
25 treatments thus reducing undesirable side effects, such as an increase in the incidence of endometrial cancers with the administration of tamoxifen (see I.N. White, *Carcinogenesis*, 20(7):1153-60, 1999; L. Bergman et al., *The Lancet*, Vol. 356, Sept. 9, 2000, 881-887) as well as the antiglucocorticoid effects and certain toxic side effects related to the administration of mifepristone (see D. Perrault et al., *J. Clin. Oncol.* 1996 Oct, 14(10),
30 pp.2709-2712; L.M. Kettel et al., *Fertil. Steril.* 1991 Sep, 56(3), pp.402-407; X. Bertagna, *Psychoneuroendocrinology* 1997, 22 Suppl. 1; pp. 51-55).

60

A further advantage of the present invention over the prior art is the provision of an effective method for the prophylaxis of hormone-dependent diseases such as breast cancer, such that patients under high risk of developing or re-developing hormone-
5 dependent diseases can be treated in advance to avoid incidence of such diseases.

In a first aspect the present invention relates to a method for the prophylaxis or treatment of breast cancer and other hormone-dependent diseases, comprising administering at least one antiprogestin, preferably antiprogestin (I) or a pharmaceutically acceptable derivative
10 or analogue thereof to a mammal, preferably a human, in need of such prophylaxis or treatment.

In a further aspect the present invention relates to the use of antiprogestins as defined above, preferably antiprogestin (I) or a pharmaceutically acceptable derivative or analogue
15 thereof, for the manufacture of a medicament, in particular for the prophylaxis or treatment of breast cancer or other hormone-dependent diseases.

In another aspect the present invention relates to pharmaceutical compositions comprising at least one antiprogestin as defined above, preferably antiprogestin (I) or a
20 pharmaceutically acceptable derivative or analogue thereof. Optionally the antiprogestin (I) can be combined with other pharmacologically active agents. For example, the antiprogestin may also be combined with a cytotoxic agent for treatment by coupling to a hormone receptor.

25 The manufacture of the medicaments may be performed according to methods known in the art. Commonly known and used adjuvants as well as further suitable carriers or diluents may be used. Suitable carriers and adjuvants may be such as recommended for pharmacy, cosmetics and related fields in: *Ullmann's Encyclopedia of Technical Chemistry*, Vol. 4, (1953), pp. 1-39; *Journal of Pharmaceutical Sciences*, Vol. 52 (1963),
30 p. 918ff; H.v.Czetsch-Lindenwald, "Hilfsstoffe für Pharmazie und angrenzende Gebiete";

Pharm. Ind. 2, 1961, p.72ff; Dr. H.P. Fiedler, *Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete*, Cantor KG, Aulendorf in Württemberg, 1971.

Antiprogestins suitable for the purposes of the present invention, preferably antiprogestin
5 (I) or a pharmaceutically acceptable derivative or analogue thereof, can be incorporated
into pharmaceutical compositions according to known methods of preparing galenics for
oral or parenteral, e.g., intraperitoneal, intramuscular, subcutaneous or percutaneous
application. They can also be implanted into tissue. Implants can comprise as inert
materials e.g. biologically degradable polymers or synthetic silicones such as e.g. silicone
10 rubber.

They can be administered in the form of tablets, pills, dragees, gel capsules, granules,
suppositories, implants, injectable sterile aqueous or oily solutions, suspensions or
emulsions, ointments, creams, gels or by intravaginal (e.g. vaginal rings) or intrauterine
15 systems (e.g., diaphragms, loops).

For the preparation of pharmaceutical compositions for oral administration, the
antiprogestins suitable for the purposes of the present invention as defined above can be
admixed with commonly known and used adjuvants and carriers such as for example, gum
20 arabic, talcum, starch, sugars such as, e.g., mannitose, methyl cellulose, lactose, gelatin,
surface-active agents, magnesium stearate, aqueous or non-aqueous excipients, paraffin
derivatives, cross-linking agents, dispersants, emulsifiers, lubricants, conserving agents
and flavoring agents (e.g., ethereal oils). In the pharmaceutical composition, the
antiprogestin may be dispersed in a microparticle, e.g. a nanoparticulate, composition.

25 In order to further enhance the bioavailability of the active agent, the antiprogestins
suitable for the purposes of the present invention as defined above can also be formulated
as cyclodextrin clathrates by reacting them with α -, β - or γ -cyclodextrines or derivatives
thereof according to the method as disclosed in PCT/EP95/02656.

For parenteral administration the antiprogestins suitable for the purposes of the present invention as defined above can be dissolved or suspended in a physiologically acceptable diluent, such as, e.g., oils with or without solubilizers, surface-active agents, dispersants or emulsifiers. As oils for example and without limitation, olive oil, peanut oil, cottonseed
5 oil, soybean oil, castor oil and sesame oil may be used.

The amount to be administered (i.e., a "pharmaceutically effective amount") varies within a broad range and depends on the condition to be treated and the mode of administration.

It can cover any amount efficient for the intended treatment. Determining a
10 "pharmaceutically effective amount" is within the purview of the person skilled in the art.

One unit dose may represent about 0.1 to 100 mg active agent(s). For administration to humans, the daily dose of the active agent(s) is about 0.1 to 400 mg, preferably 10 to 100
15 mg, most preferably 50 mg.

15

The pharmaceutical compositions according to the present invention can also be administered via a depot injection, an implant preparation or an IUD (internal uterine device), optionally for sustained delivery of the active agent(s).

20 The preferred mode of administration is oral administration. The antiprogestins for use according to the invention, and in particular, antiprogestin (I) or a pharmaceutically acceptable derivative or analogue thereof are particularly suitable for oral administration.

According to all aspects of the present invention it is also possible to combine at least one
25 antiprogestin as defined above, in particular antiprogestin (I) or a pharmaceutically acceptable derivative or analogue thereof, with at least one antiestrogen, because many hormone-dependent diseases, in particular breast cancer, exhibit not only progesterone receptors, but also estrogen receptors. The antiestrogen may be administered either simultaneously with or sequentially to the antiprogestin, and in particular with/to
30 antiprogestin (I) or a pharmaceutically acceptable derivative or analogue thereof. The amount of antiprogestin and antiestrogen may be equal or one component may be more

63
predominant than the other, such as in an antiprogesterin:antiestrogen ratio of 1:50 to 50:1, preferably 1:30 to 30:1, and most preferably 1:15 to 15:1.

Examples of suitable antiestrogens for use according to the invention are non-steroidal
5 antiestrogens, such as tamoxifen and nafoxidine as well as raloxifen and EM800 and the
steroidal antiestrogen faslodex. Examples of steroidal antiestrogens include those
disclosed in EP 0 348 341 A and those disclosed in WO 98/07740, in particular, 11 β -
flouro-7 α -{5-[N-methyl-N-3-(4,4,5,5,5-pentafluoropentylthio-propylamino)-pentyl]}-
estra-1,3,5(10)-trien-3,17 β -diol, or those disclosed in WO 99/33855, in particular 11 β -
10 flouro-7 α -{5-[methyl-(7,7,8,8,9,9,10,10,10-nonafluoro-decyl)-amino]-pentyl}-estra-
1,3,5(10)-trien-3,17 β -diol or pharmaceutically acceptable derivatives or analogues
thereof. Aromatase inhibitors having an antiestrogenic effect, such as those disclosed on
pages 7 to 8 of EP 0 495 825 B1 may also be used as antiestrogens.

15 The invention is further illustrated in the examples. The following examples are not to be
understood as a limitation.

Examples

20 Example 1:

DMBA-induced breast cancer model in rat (prevention experiment)

Materials and Methods:

25 Immature female Sprague-Dawley rats (49 - 51 days old; 10 animals/group) were used in
this study. The carcinogen 7,12-dimethylbenz[a]anthracene (DMBA) was given as a
single oral administration (10 mg). Treatment was started 20 days later as followed: 1)
solvent control, 2) ovariectomy at treatment start, 3) tamoxifen, 1 mg/kg s.c., 4)
antiprogesterin (I), 3 mg/kg, s.c., 6 days/week. Rats were examined weekly for breast
30 tumors by palpation. As a parameter for the prophylactic effect the tumor incidence
(number of animals/group with tumors in %) was determined. For a further description

and evaluation of DMBA and NMU prevention models, see R.G. Metha, *European Journal of Cancer* 36 (2000), pp. 1275-1282.

Results:

5

In the control group all rats developed mammary tumors within 10 weeks after treatment start (incidence 100%) and progressive tumor growth was observed. Prophylactic treatment with the antiprogesterin (I) prevented the tumor development for 12 weeks completely, and at the end of the experiment, after 22 weeks, in only one rat a tumor was detected (incidence 10%). After ovariectomy at the end of the experiment 40% of the rats had developed tumors. In comparison, treatment with the antiestrogen tamoxifen reduced the tumor incidence only to 60% (see fig. 1)

Conclusion:

15

In the DMBA-induced mammary tumor model in the rat, the antiprogesterin (I) completely suppressed the tumor development in intact animals for more than 12 weeks after treatment start. Figure 1 clearly shows the superiority in activity of antiprogesterin (I) over the conventional anti-breast cancer reagent tamoxifen and even over standard estrogen deprivation therapy (ovariectomy) with respect to prophylactic treatment. Antiprogesterin (I) is thus superior to the established standard therapy for preventing breast cancer in women under high risk of developing the disease (tamoxifen prophylactic therapy).

20

These and the following results indicate that the use of antiprogesterin (I) for the prophylaxis and treatment of breast cancer is superior to established standard treatments.

25

Example 2:DMBA-induced breast cancer model in rat (therapy experiment/dose-response study)

Materials and Methods:

5

Immature female Sprague-Dawley rats (49 - 51 days old; 10 animals/group) were used in this study. Mammary tumors were induced by a single oral administration of 10 mg 7,12-dimethylbenz[a]anthracene (DMBA, Serva/Heidelberg). Rats with at least one established

tumor with a size of more than 150 mm² were treated for 4 weeks by: 1) solvent control, 2) ovariectomy at treatment start, 3) antiprogesterin (I), 0.5 mg/kg s.c., 4) antiprogesterin (I), 2 mg/kg s.c., 5) antiprogesterin (I), 5 mg/kg s.c., 6) antiprogesterin (I), 10 mg/kg s.c., and 7) onapristone, 5 mg/kg, s.c., daily. As a parameter for growth inhibition the change of tumor area (in % with respect to initial tumor size) determined by weekly caliper measurements was used. For statistical analysis of intergroup differences of mean values the Kruskal-

15 Wallis-test was used.

Results:

In intact control animals, progressive tumor growth was observed, whereas ovariectomy caused a considerable tumor regression in 90% of the animals. Treatment with antiprogesterin (I) at doses of or above 2 mg/kg resulted in a significant inhibition of tumor growth compared with the control (see fig. 2). There was a clear dose-response relationship. Whereas treatment with 0.5 mg/kg antiprogesterin (I) did not significantly prevent the tumor from growing, at 2 mg/kg maximal growth inhibition was observed. In this group a complete tumor regression was seen in 50% of the rats. The effect of the highest dose of antiprogesterin (I) tested in this experiment (10 mg/kg), was comparable to that of 2 mg/kg. Onapristone (5 mg/kg, s.c.) was distinctly less effective than antiprogesterin (I) at comparable doses.

30

Conclusion:

In the DMBA-induced mammary tumor model in the rat, antiprogesterin (I) completely suppresses the tumor growth in intact animals. It was found that 2 mg/kg antiprogesterin (I) has a maximal effect on tumor growth. Antiprogesterin (I) was distinctly superior to onapristone.

Example 3:

10 NMU-induced breast cancer model in rat (prevention experiment)

Materials and Methods:

Tumors were induced by a single intravenous injection of NMU (nitrosomethylurea; 50 mg/kg) in female Sprague-Dawley rats (obtained from Tierzucht Schönwalde, age 50-55 days). Treatment was started 10 days later as followed: 1) solvent control, 2) ovariectomy at treatment start, 3) tamoxifen, 3 mg/kg s.c., 4) antiprogesterin (I), 3 mg/kg, s.c., 5) letrozole, 3 mg/kg s.c., 6) raloxifen, 3 mg/kg s.c., 6 days/week. Rats were examined weekly for breast tumors by palpation. As a parameter for the prophylactic effect the tumor incidence (number of animals/group with tumors in %) was determined. For a further description and evaluation of DMBA and NMU prevention models, see R.G. Metha, *European Journal of Cancer* 36 (2000), pp. 1275-1282.

Results:

25

In the control group all rats developed mammary tumors within 10 weeks after treatment start (incidence 100%; see fig. 3) and progressive tumor growth was observed.

Prophylactic treatment with the antiprogesterin (I) prevented the tumor development for 12 weeks completely, and at the end of the experiment, after 27 weeks, in only one rat a tumor was detected (incidence 10%). In comparison, in treatment with the other antiestrogens or the aromatase inhibitor letrozole the tumor incidence was reduced only to

20 - 60%. After ovariectomy at the end of the experiment 20% of the rats had developed tumors.

Conclusion:

5

In the NMU-induced mammary tumor model in the rat, antiprogesterone (I) completely suppressed the tumor development in intact animals for more than 12 weeks after treatment start. The effect of the prophylactic treatment by antiprogesterone (I) was superior to that of conventional antiestrogens for breast cancer therapy (i.e., raloxifen, tamoxifen) and aromatase inhibitor letrozol and to standard estrogen deprivation therapy (ovariectomy) regarding tumor incidence and tumor growth.

As in the DMBA-induced tumor model (see Example 1), these results indicate that

antiprogesterone (I) effectively prevents the development of breast tumors in a manner which is superior to the standard prophylactic treatment, e.g. with tamoxifen.

Example 4:

NMU-induced breast cancer model in rat (therapy experiment)

20

Materials and Methods:

Tumors were induced by a single intravenous injection of NMU (nitrosomethylurea, 50 mg/kg) in female Sprague-Dawley rats (obtained from Tierzucht Schönwalde, age 50-55 days). Starting 10 days later, rats with at least one established tumor were treated for 4 weeks by: 1) solvent control, 2) ovariectomy at treatment start, 3) antiprogesterone (I), 1.0 mg/kg/day, 4) antiprogesterone (I), 0.5 mg/kg/day and 5) onapristone, 5 mg/kg/day. As a parameter for growth inhibition the change of tumor area (in % of initial tumor size) determined by weekly caliper measurements was used. For statistical analysis of intergroup differences of mean values the Kruskal-Wallis-test was used.

Results:

In intact control animals, progressive tumor growth was observed, whereas ovariectomy caused a complete tumor growth inhibition. Treatment with antiprogesterin (I) at doses of 0.5 or 1.0 mg/kg resulted in a significant inhibition of tumor growth compared with the control (see fig. 4). Onapristone (5 mg/kg) was distinctly less effective than antiprogesterin (I) at the much lower dose of 0.5 mg/kg.

Conclusions:

In the MNU-induced mammary tumor model in the rat, antiprogesterin (I) completely suppresses the tumor growth in intact animals. It was found that at a dose of 1.0 mg/kg and even at a dose of only 0.5 mg/kg antiprogesterin (I) has a significant effect on tumor growth. Thus, antiprogesterin (I) was superior to known antiprogesterins like onapristone.

Example 5:

T47D Human xenograft (therapy experiment)

Materials and Methods:

Female Fox Chase scid mice (M&B) were supplemented with estradiol pellets (Innovative Research of America). T47D breast cancer cells, obtained from cell culture and suspended in matrigel, were implanted s.c. in the inguinal region of the mice. Treatment was started when the tumors were approximately 25 mm² in size. Treatment was continued until progression of the tumors. Experimental groups were: 1) control (vehicle), 2) ovariectomy, 3) antiprogesterin (I), 10 mg/kg s.c.. Tumor area was determined by caliper measurements. The Kruskal Wallis test was used for statistical analysis of intergroup differences of mean values.

Results:

In the T47D breast cancer model, ovariectomy resulted in a considerable inhibition of tumor growth, compared with the rapid growth in the control. Fig. 5 shows that the s.c. application of 10 mg/kg antiprogesterin (I) also caused an inhibition of tumor growth, almost comparable to the effect of conventional estrogen deprivation therapy (ovariectomy).

Conclusion:

The effect of antiprogesterin (I) in inhibiting the growth of the human T47D breast cancer xenografted in Fox Chase scid mice is comparable to the effect of standard estrogen deprivation therapy (ovariectomy) which is considered to be the maximum effective method of inhibiting growth of breast cancer in this model.

Example 6:

MCF7 Human xenograft (therapy experiment)

Materials and Methods:

Female Fox Chase scid mice (M&B) were supplemented with estradiol pellets (Innovative Research of America). MCF7 breast cancer cells, obtained from cell culture and suspended in matrigel, were implanted s.c. in the inguinal region of the mice. Treatment was started when the tumors were approximately 25 mm² in size. Treatment was continued until progression of the tumors. Experimental groups were: 1) control (vehicle), 2) ovariectomy, 3) antiprogesterin (I), 10 mg/kg s.c. Tumor area was determined by caliper measurements. The Kruskal Wallis test was used for statistical analysis of intergroup differences of mean values.

Results:

In the MCF7 breast cancer model, ovariectomy resulted in a considerable inhibition of tumor growth, compared with the rapid growth in the control. Fig. 6 shows that the s.c. application of 10 mg/kg antiprogesterin (I) also caused an inhibition of tumor growth, almost comparable to the effect of conventional estrogen deprivation therapy (ovariectomy).

Conclusion:

The effect of antiprogesterin (I) in inhibiting the growth of the human MCF7 breast cancer xenografted in Fox Chase scid mice is comparable to the effect of standard estrogen deprivation therapy (ovariectomy) which is considered to be the maximum effective method of inhibiting growth of breast cancer in this model.

CLAIMS

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1. Use of the antiprogesterin 11β -(4-acetylphenyl)- 17β -hydroxy- 17α -(1,1,2,2,2-pentafluoroethyl)-estra-4,9-dien-3-one or a pharmaceutically acceptable derivative or analogue thereof for the manufacture of a medicament for the prophylaxis or treatment of a hormone-dependent disease in a mammal.

10

2. Use according to claim 1, wherein the disease is breast cancer.

3. Use according to claims 1 or 2, wherein the mammal is a human.

15

4. Use according to any preceding claim, wherein the medicament is administered orally.

20

5. Use according to any preceding claim, wherein the antiprogesterin 11β -(4-acetylphenyl)- 17β -hydroxy- 17α -(1,1,2,2,2-pentafluoroethyl)-estra-4,9-dien-3-one is administered in a unit dose of 50 mg.

25

6. Pharmaceutical composition comprising the antiprogesterin 11β -(4-acetylphenyl)- 17β -hydroxy- 17α -(1,1,2,2,2-pentafluoroethyl)-estra-4,9-dien-3-one or a pharmaceutically acceptable derivative or analogue thereof in an amount sufficient for the prophylaxis or treatment of a hormone-dependent disease in a mammal.

30

7. Pharmaceutical composition according to claim 6, wherein the disease is breast cancer.

8. Pharmaceutical composition according to claims 6 or 7, wherein the mammal is a human.
 9. Pharmaceutical composition according to any one of claims 6 to 8, further comprising an antiestrogen.
- 5

ABSTRACT

The present invention relates to methods and uses for preventing or treating hormone-dependent disease, in particular breast cancer, in a mammal by antiprogestins, in particular
5 antiprogestin 11β -(4-acetylphenyl)- 17β -hydroxy- 17α -(1,1,2,2,2-pentafluoroethyl)-estra-4,9-dien-3-one or a pharmaceutically acceptable derivative or analogue thereof. The invention further relates to pharmaceutical compositions comprising said antiprogestin.

FIG. 1

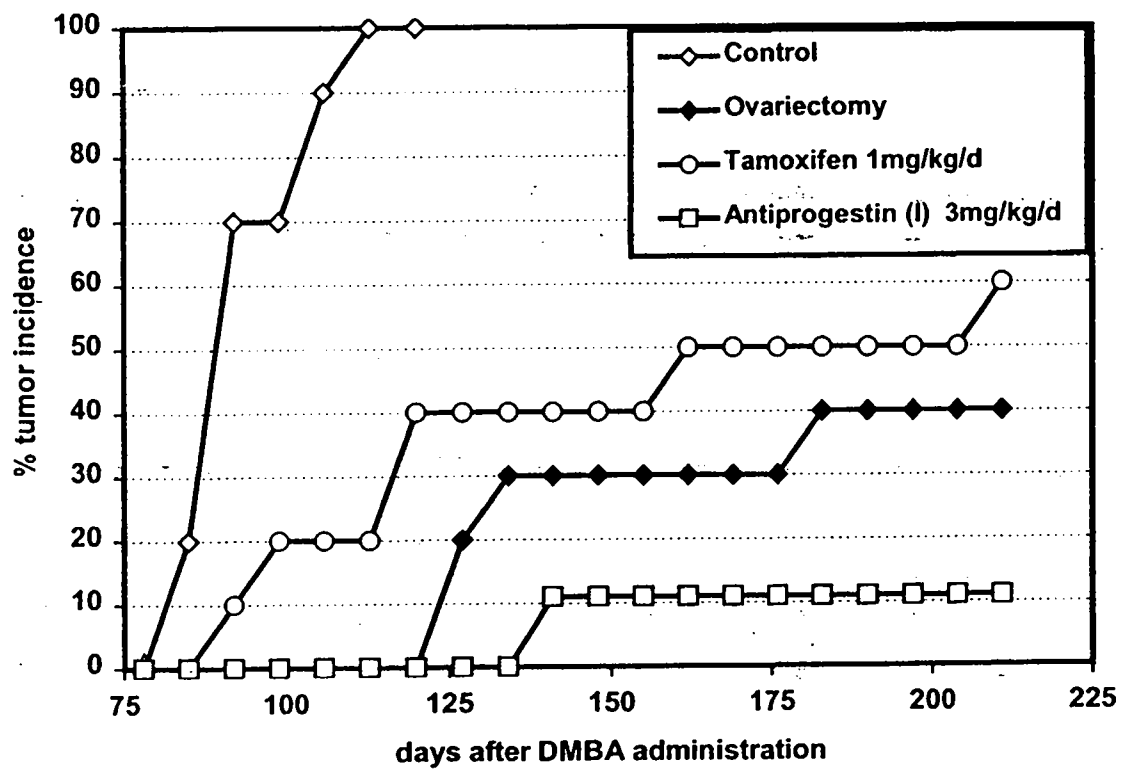


FIG. 2

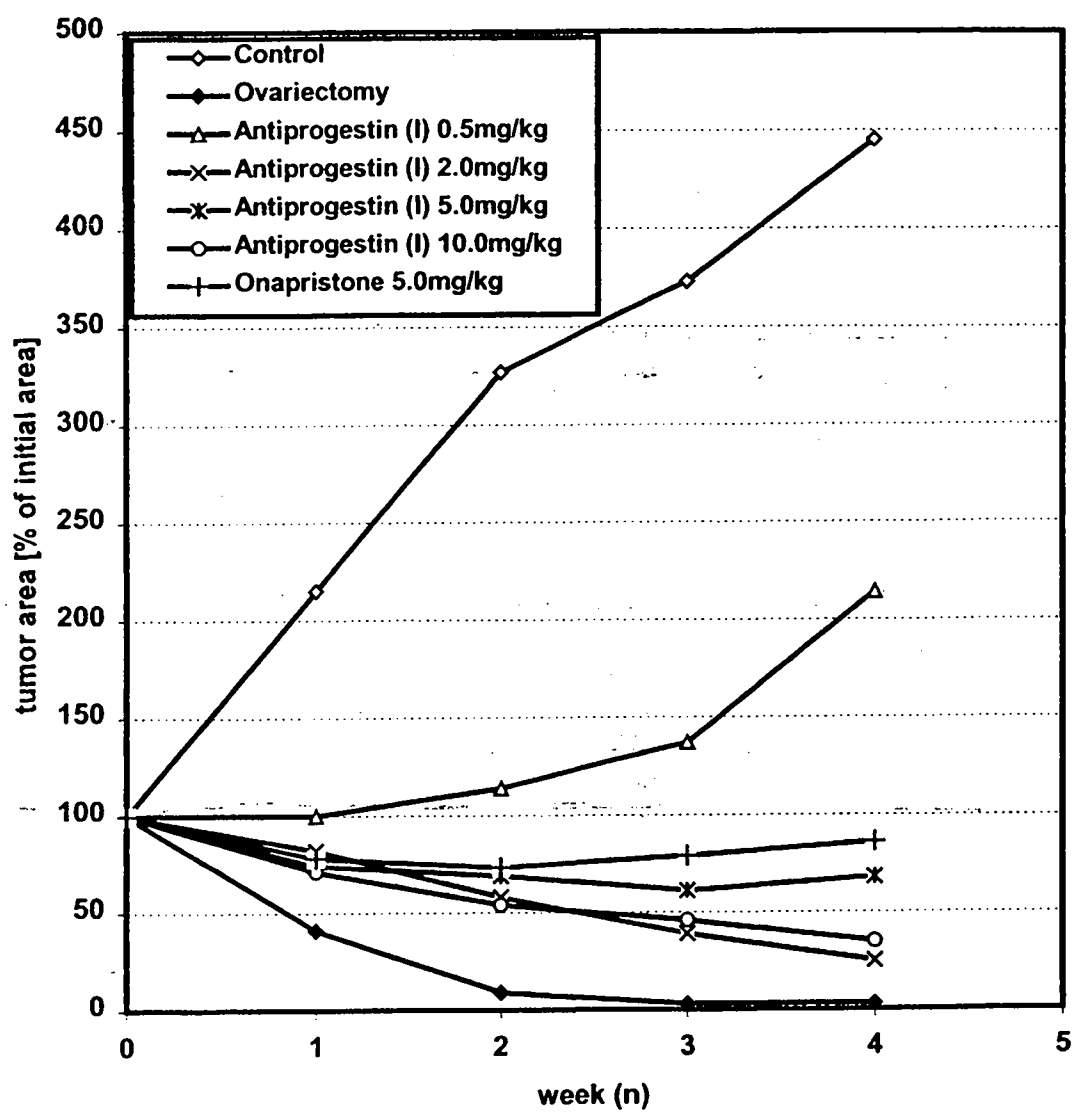


FIG. 3

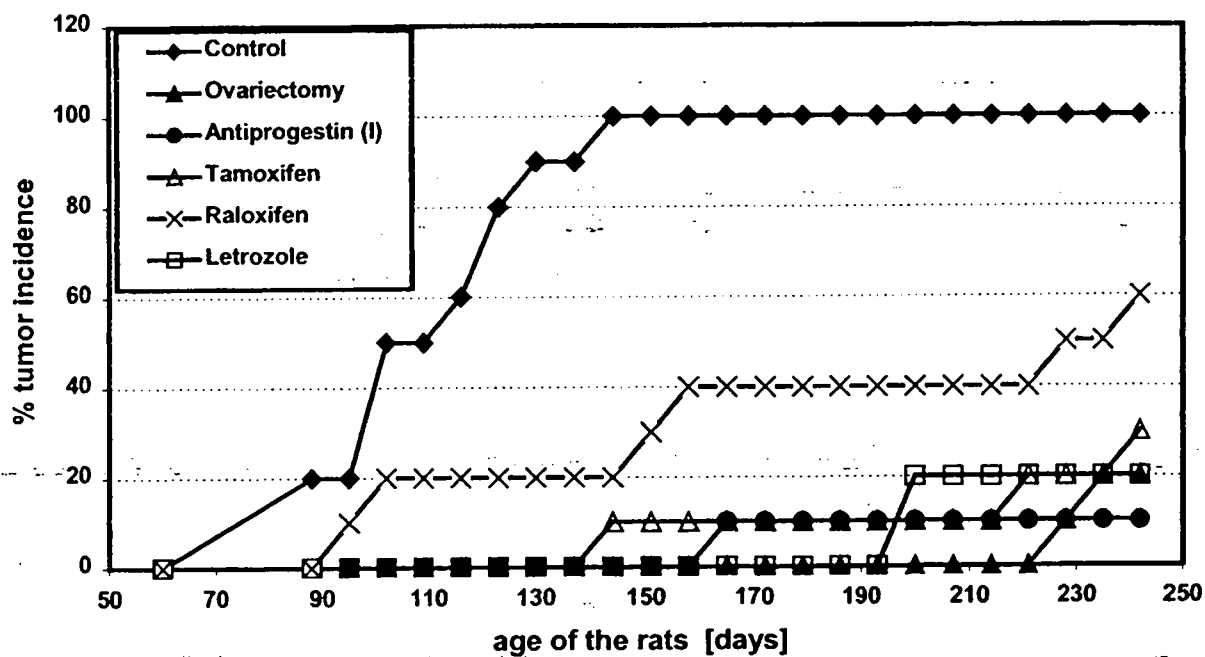


FIG. 4

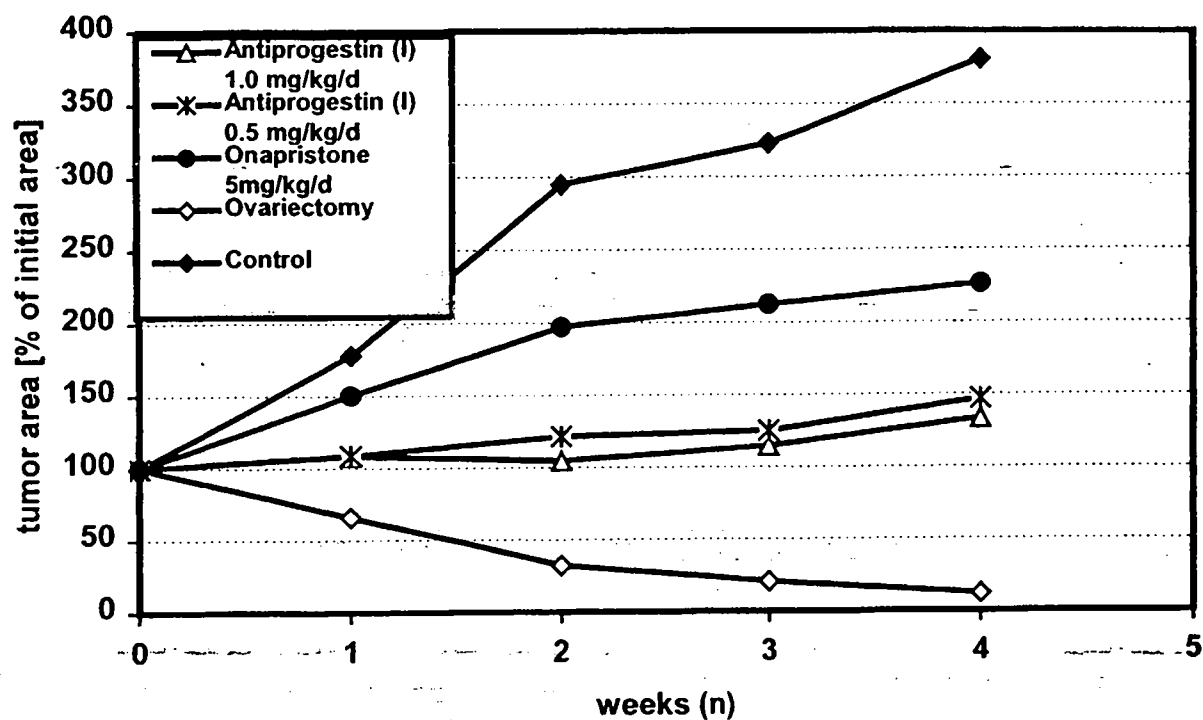


FIG. 5

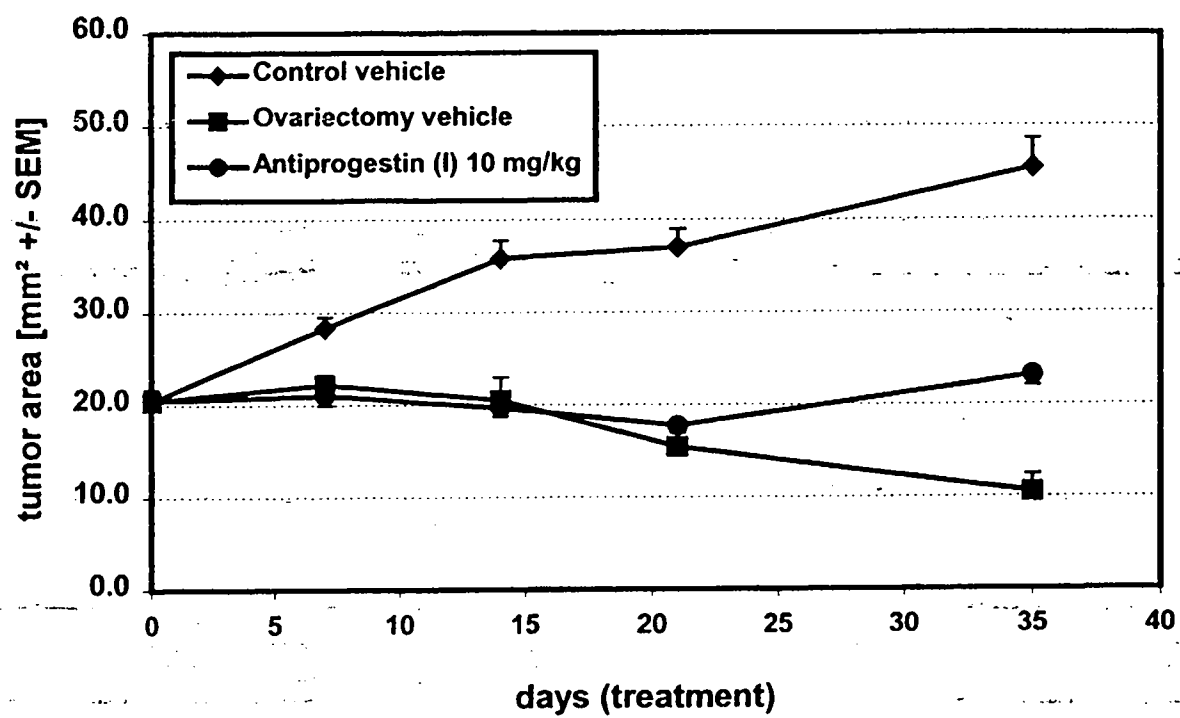
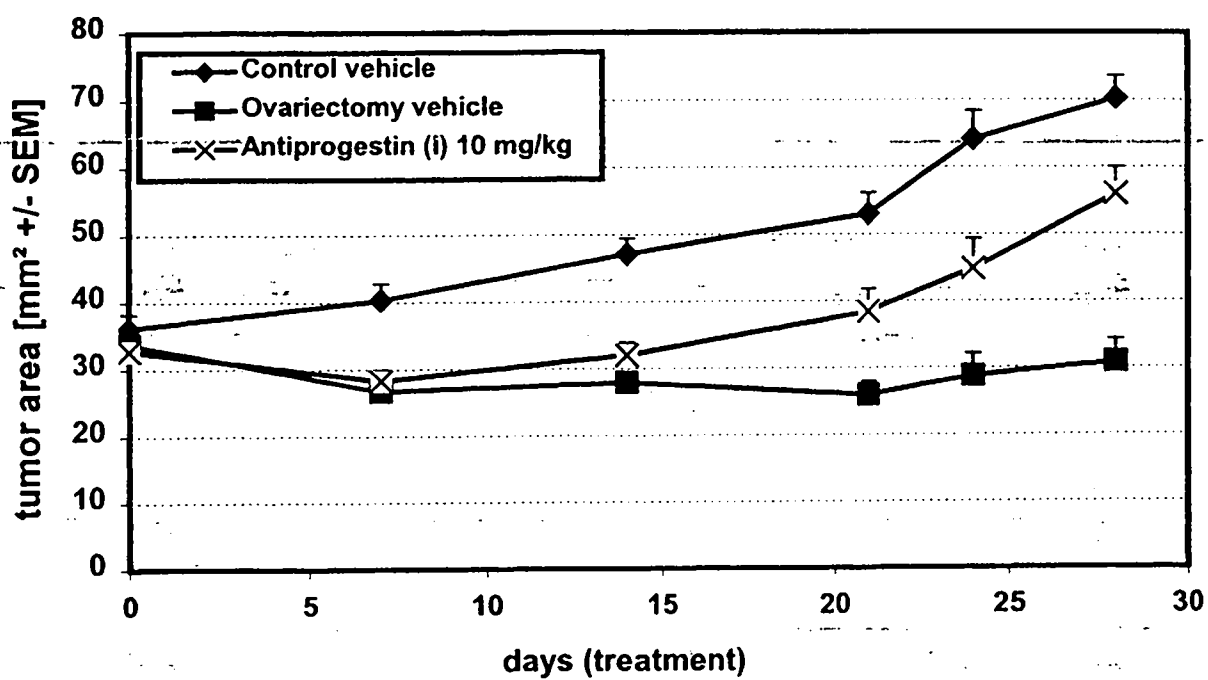


FIG. 6



USO DE ANTIPROGESTINAS PARA LA PROFILAXIS Y EL TRATAMIENTO DE ENFERMEDADES DEPENDIENTES DE HORMONAS

Campo de la invención

La presente invención se relaciona con el uso de anti-progestinas para la profilaxis y el tratamiento de enfermedades dependientes de hormonas, en particular, cáncer de mama. La presente invención se relaciona además con composiciones farmacéuticas y formas de dosificación que comprenden antiprogestinas para la profilaxis y el tratamiento de enfermedades dependientes de hormonas, en particular cáncer de mama. Una antiprogestina particularmente preferida para usar en la invención es la antiprogestina 11β -(4-acetilfenil)- 17β -hidroxi- 17α -(1,1,2,2,2-pentafluoroetil)-estra-4,9-dien-3-ona, o un derivado o análogo de la misma aceptable para uso farmacéutico.

Antecedentes de la invención

La terapia endócrina representa un paradigma de tratamiento eficaz, mínimamente tóxico, paliativo para el cáncer de mama metastásico. Como tratamiento paliativo común para carcinomas mamarios no operables, así como coadyuvante en terapia después del tratamiento primario de carcinomas mamarios no operables, se usa el antiestrógeno tamoxifen. Sin embargo, el tamoxifen no puede curar el cáncer de mama. Así, para la terapia secundaria, se usan comúnmente progestinas o inhibidores de aromatasa. En la ovariectomía de mujeres pre-

menopáusicas, los análogos de tamoxifen y LHRH (hormona liberadora de hormona luteinizante) logran resultados comparables (H.T. Mouridsen et al., *Eur. J. Cancer Clin. Oncol.*, 24, páginas 99-105, 1988).

Aunque el tamoxifen se usa ampliamente como coadyuvante en terapia para el cáncer de mama, su uso como agente quimiopreventivo es problemático, ya que se ha demostrado que el tratamiento resulta en un aumento en la incidencia de cánceres de endometrio (I.N.White, *Carcinogenesis*, 20(7): 1153-60, 1999).

Las antiprogestinas representan una clase relativamente nueva y prometedora de agentes terapéuticos que podrían tener un impacto significativo en el tratamiento de tumores dependientes de hormonas y otras enfermedades. Aunque las antiprogestinas fueron creadas originalmente para la terminación medicinal no quirúrgica del embarazo, algunas antiprogestinas han ganado una importancia considerable, p.ej., en la terapia en aquellos cánceres de mama que poseen receptores para progesterona (T. Maudelonde et al., en: J.G.M. Klijn et al., *Hormonal Manipulation of Cancer: Peptides, Growth Factors and New (Anti) Steroidal Agents*, Raven Press, Nueva York, 1987, páginas 55-59). Esta nueva estrategia en terapia endócrina se basa en la actividad antitumoral de las antiprogestinas en las líneas de células humanas de cáncer de mama positivas para receptores *in vitro* y en varios tumo-

res mamarios dependientes de hormonas de ratón y rata *in vivo*. En particular, el mecanismo antitumoral de las antiprogestinas onapristona y mifepristona (RU 486) ya ha sido investigado usando el modelo de tumor mamario MXT dependiente de hormonas, así como los modelos de tumores mamarios inducidos por DMBA y NMU en rata (M. R. Schneider et al., *Eur. J. Cancer Clin. Oncol.*, Volumen 25, N° 4, páginas 691-701, 1989; H. Michna et al., *Brest Cancer Research and Treatment* 14:275-288, 1989; H. Michna, *J.Steroid.Biochem.* Volumen 34, N° 1-6, páginas 447-453, 1989). Sin embargo, debido a la baja actividad y a los efectos colaterales adversos relacionados con, p.ej., la mifepristona, no pudo recomendarse este compuesto como agente individual en el manejo del cáncer de mama (D.Perrault et al., *J.Clin.Oncol.* 1996 Oct, 14(10), pág. 2709-2712).

Los compuestos de antiprogestina son adecuados para iniciar abortos y, así, para usarlos en el control de fertilidad postcoital, como anticonceptivos para mujeres (WO-A 93/23020, WO-A 93/21927) y, además, para el tratamiento de irregularidades hormonales, para iniciar la menstruación y para iniciar el trabajo de parto. Otras indicaciones son en el campo de la terapia de sustitución de hormonas (WO-A 94/18983), el tratamiento de afecciones relacionadas con la dismenorrea y el tratamiento de endometriosis (EP-A 0 266 303), así como miomas.

Los 17α -fluoroalquilesteroides que tienen una fuerte actividad antiprogestina, así como los métodos para producirlos, se describen en WO 98/34947.

Las antiprogestinas de la técnica previa evaluadas o usadas previamente debido a su actividad antitumoral muestran algunas desventajas.

Por ej., a pesar del hecho de que las antiprogestinas de la técnica previa mostraron actividad antigestagénica, estos compuestos no resultaron tratamientos adecuados para enfermedades dependientes de hormonas tales como el cáncer de mama. En particular, los compuestos de la técnica previa se asociaron con efectos colaterales, p.ej., la mifepristona muestra fuertes efectos colaterales antiglucocorticoides (véanse L.M. Kettel et al., *Fertil.Steril.* 1991 Sep, 56(3), páginas 402-407; X. Bertagna, *Psychoneuroendocrinology* 1997; 22 Suplemento 1, pág.51-55) y, además, mostró solamente una actividad moderada en ensayos clínicos (véase nuevamente D. Perrault et al., *J.Clin.Oncol.* 1996 Oct, 14(10), pág.2709-2712). Respecto de efectos colaterales de otras terapias basadas en hormonas, como ya se mencionó previamente, la administración de tamoxifen puede resultar en un aumento en la incidencia de cánceres de endometrio (I.N.White, *Carcinogenesis*, 20(7):1153-60, 1999).

Otro problema con las antiprogestinas de la técnica previa era su biodisponibilidad pobre cuando se las adminis-

traba por vía oral. Así, generalmente tenían que administrarse en altas dosis, dando lugar a posibles efectos colaterales desfavorables. Más aún, la administración oral es deseable respecto de la conveniencia y el seguimiento por parte del paciente.

Además, existe aún una necesidad de compuestos que sean activos no solamente en el tratamiento, pero también en la profilaxis del cáncer de mama y otras enfermedades dependientes de hormonas. La incidencia incrementada de cáncer de endometrio asociada con el tamoxifen tiende a mostrar que este compuesto no es adecuado para el tratamiento de profilaxis de mujeres saludables, y no existen otros compuestos adecuados disponibles (véase L. Bergman et al., *The Lancet*, Vol. 356, Sept. 9, 2000; 881-887).

Objeto de la presente invención

Es un objeto de la presente invención prevenir o reducir las desventajas de los métodos de la técnica previa para prevenir o tratar enfermedades dependientes de hormonas, tales como el cáncer de mama. Se desea especialmente que el medio que se provee para prevenir y tratar enfermedades dependientes de hormonas, tales como cáncer de mama, mediante la administración de agentes altamente efectivos, sea superior a los métodos y agentes conocidos, incluyendo la ovariectomía. Así, se desea especialmente además proveer un tratamiento de enfermedades dependientes de hormonas, tales como el cán-

cer de mama, que evite la severa cirugía altamente riesgosa asociada con la ovariectomía. Se desea además proveer un agente para usar de acuerdo con la invención que muestre menos efectos colaterales que los métodos previamente conocidos o sugeridos para tratar y prevenir enfermedades dependientes de hormonas tales como el cáncer de mama.

Es otro objeto de la presente invención proveer composiciones farmacéuticas que comprenden agentes antitumorales altamente efectivos para la profilaxis y el tratamiento del cáncer de mama y de otras enfermedades dependientes de hormonas.

Estos objetos se logran sorprendentemente mediante el uso de antiprogestinas de acuerdo con la presente invención y a través de composiciones farmacéuticas y formas de dosificación que comprenden tales antiprogestinas. Es particularmente preferida en este caso la antiprogestina 11β -(4-acetilfenil)- 17β -hidroxi- 17α -(1,1,2,2,2-pentafluoroetil)-estra-4,9-dien-3-ona o un derivado o análogo de la misma aceptable para uso farmacéutico.

Es otro objeto de la presente invención proveer antiprogestinas, tales como la antiprogestina 11β -(4-acetilfenil)- 17β -hidroxi- 17α -(1,1,2,2,2-pentafluoroetil)-estra-4,9-dien-3-ona o derivados o análogos de la misma aceptables para uso farmacéutico, que sean particularmente adecuadas para administración oral.

Resumen de la invención

La presente invención se basa en la nueva e inesperada observación de que algunas antiprogestinas, en particular 11β -(4-acetilfenil)- 17β -hidroxi- 17α -(1,1,2,2,2-pentafluoroetil)-estra-4,9-dien-3-ona, o un derivado o análogo de la misma aceptable para uso farmacéutico, es excepcionalmente activa en la prevención y la reducción del crecimiento tumoral en los modelos de cáncer de mama inducidos por DMBA (7,12-dimetilbenzantraceno) y NMU (N-metilnitrosourea). De hecho, la antiprogestina 11β -(4-acetilfenil)- 17β -hidroxi- 17α -(1,1,2,2,2-pentafluoroetil)-estra-4,9-dien-3-ona (I) resultó ser distintivamente más potente que el tamoxifen y la ovariectomía en la prevención del desarrollo de cáncer de mama.

Así, la presente invención provee un método para la profilaxis y el tratamiento de cáncer de mama y otras enfermedades dependientes de hormonas en mamíferos, en particular humanos, que necesitan de tal tratamiento, que comprende administrar una cantidad efectiva para uso farmacéutico de una antiprogestina, en particular 11β -(4-acetilfenil)- 17β -hidroxi- 17α -(1,1,2,2,2-pentafluoroetil)-estra-4,9-dien-3-ona, o un derivado o análogo de la misma aceptable para uso farmacéutico, a un paciente.

La presente invención provee además composiciones farmacéuticas que comprenden una antiprogestina, en particular 11β -(4-acetilfenil)- 17β -hidroxi- 17α -(1,1,2,2,2-pentafluoro-

etil)-estra-4,9-dien-3-ona, o un derivado o análogo de la misma aceptable para uso farmacéutico, en una cantidad suficiente para la profilaxis o el tratamiento de cáncer de mama u otras enfermedades dependientes de hormonas.

La antiprogestina preferida 11β -(4-acetilfenil)- 17β -hidroxi- 17α -(1,1,2,2,2-pentafluoroetil)-estra-4,9-dien-3-ona se conocerá de aquí en adelante como "antiprogestina (I)".

Breve descripción de las figuras

La figura 1 muestra el efecto de prevención de desarrollo de tumores de la antiprogestina (I) en el carcinoma mamario de rata inducido por DMBA, en comparación con un control, tamoxifen y ovariectomía.

La figura 2 muestra los efectos inhibidores del crecimiento tumoral de la antiprogestina (I) en un estudio de respuesta a la dosis en el carcinoma mamario de rata inducido por DMBA, en comparación con un control, la antiprogestina onapristona, así como una ovariectomía. El estudio se realizó con dosis de 0,5, 2,0, 5,0 y 10,0 mg/kg s.c. de antiprogestina (I).

La figura 3 muestra el efecto de prevención del desarrollo tumoral de la antiprogestina (I) en el carcinoma mamario de rata inducido por NMU, en comparación con un control, los antiestrógenos raloxifen y tamoxifen, el inhibidor de la aromatasa letrozol, así como ovariectomía.

La figura 4 muestra el efecto inhibidor del crecimiento

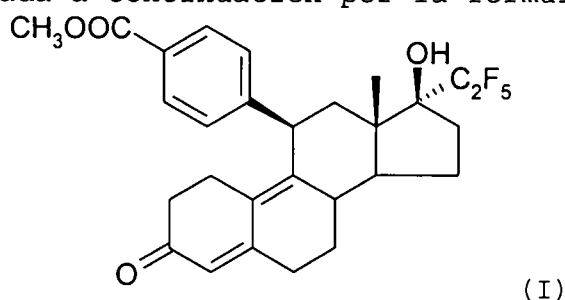
tumoral de dosis de 0,5 y 1,0 mg/kg de antiprogestina (I) en el carcinoma mamario de rata inducido por NMU, en comparación con un control, onapristona (5 mg/kg) y ovariectomía.

La figura 5 muestra el efecto inhibidor del crecimiento tumoral de la antiprogestina (I) en una dosis de 10 mg/kg s.c. en el modelo de xenoinjerto T47D humano en ratones SCID, en comparación con un control, así como ovariectomía.

La figura 6 muestra el efecto inhibidor del crecimiento tumoral de la antiprogestina (I) en una dosis de 10 mg/kg s.c. en el modelo de xenoinjerto MCF7 humano en ratones SCID, en comparación con un control, así como ovariectomía.

Descripción detallada de la invención

La antiprogestina (I) - 11β -(4-acetilfenil)- 17β -hidroxi- 17α -(1,1,2,2,2-pentafluoroetil)-estra-4,9-dien-3-ona - está representada a continuación por la fórmula (I):



La antiprogestina (I) (o un derivado o análogo de la misma aceptable para uso farmacéutico) es un agente farmacéutico valioso que tiene una fuerte actividad antiprogestina. La antiprogestina (I) puede usarse de acuerdo con la presente invención para la profilaxis y el tratamiento del

cáncer de mama y otras enfermedades dependientes de hormonas.

El término "antiprogestina" en el contexto de la presente invención pretende comprender primariamente todos los compuestos que son capaces de inhibir competitivamente los receptores de progesterona. Sin embargo, debería abarcar también compuestos capaces de inhibir la biosíntesis de progestinas.

Los derivados o análogos aceptables para uso farmacéutico de la antiprogestina (I) en el contexto de la presente invención pueden incluir, p.ej., cualquiera de los compuestos de la invención que se describen en WO 98/34947.

El término "enfermedades dependientes de hormonas", en el contexto de la presente invención, puede incluir, sin limitaciones, cáncer de mama, cáncer de ovario, cáncer de endometrio, mieloma, infertilidad anovulatoria, meningioma, es decir, enfermedades que se originan o están influidas sustancialmente por la presencia de receptores de hormonas y/o vías dependientes de hormonas.

Respecto de la superioridad de la presente invención sobre la técnica previa, es especialmente favorable que, p.ej., con la antiprogestina (I), usada de acuerdo con la presente invención, los efectos colaterales endócrinos adicionales, tales como, p.ej., la actividad de los andrógenos, los estrógenos o los antiglucocorticoides es solamente muy

débil, si llega a estar presente. Debido a la alta biodisponibilidad de la antiprogestina (I), puede administrársela por vía oral, tornando así el tratamiento para un paciente que lo necesita tan conveniente como sea posible. Como consecuencia favorable adicional, la antiprogestina (I) es bien tolerada y puede administrarse en dosis relativamente bajas en comparación con los tratamientos establecidos, reduciendo así los efectos colaterales indeseados, tales como un aumento en la incidencia de cánceres de endometrio con la administración de tamoxifen (véanse I.N. White, *Carcinogenesis*, 20(7):1153-60, 1999; L. Bergman et al., *The Lancet*, Vol. 356, Sept. 9, 2000, 881-887), así como los efectos antigluco-corticoides y algunos efectos colaterales tóxicos relacionadas con la administración de mifepristona (véanse D. Perrault et al., *J. Clin. Oncol.* 1996 Oct, 14(10), páginas 2709-2712; L.M. Kettel et al., *Fertil. Steril.* 1991 Sep, 56(3), páginas 402-407; X. Bertagna, *Psychoneuroendocrinology* 1997, 22 Suplemento 1; pág. 51-55).

Otra ventaja de la presente invención sobre la técnica previa es la provisión de un método efectivo para la profilaxis de enfermedades dependientes de hormonas tales como el cáncer de mama, de modo tal que los pacientes con alto riesgo de desarrollar o desarrollar nuevamente enfermedades dependientes de hormonas pueden ser tratados para evitar la incidencia de tales enfermedades.

En un primer aspecto, la presente invención se relaciona con un método para la profilaxis o el tratamiento de cáncer de mama y otras enfermedades dependientes de hormonas, que comprende administrar al menos una antiprogestina, preferiblemente antiprogestina (I) o un derivado o análogo de la misma aceptable para uso farmacéutico a un mamífero, preferiblemente a un humano, que necesita de tal profilaxis o tratamiento.

En otro aspecto, la presente invención se relaciona con el uso de antiprogestinas como se las describió previamente, preferiblemente antiprogestina (I) o un derivado o análogo de la misma aceptable para uso farmacéutico, para la fabricación de un medicamento, en particular para la profilaxis o el tratamiento de cáncer de mama u otras enfermedades dependientes de hormonas.

En otro aspecto, la presente invención se relaciona con composiciones farmacéuticas que comprenden al menos una antiprogestina como se la definió previamente, preferiblemente antiprogestina (I) o un derivado o análogo de la misma aceptable para uso farmacéutico. Opcionalmente, la antiprogestina (I) puede combinarse con otros agentes farmacológicamente activos. P.ej., la antiprogestina puede combinarse también con un agente citotóxico para un tratamiento mediante la unión a un receptor de hormonas.

La fabricación de medicamentos puede realizarse de

acuerdo con métodos conocidos en la técnica. Pueden usarse coadyuvantes, así como otros vehículos o diluyentes adecuados. Los vehículos o coadyuvantes adecuados pueden ser como se los recomienda para campos farmacéuticos, cosméticos y relacionados en: *Ullmann's Encyclopedia of Technical Chemistry*, Volumen 4, (1953), páginas 1-39; *Journal of Pharmaceutical Sciences*, Volumen 52 (1963), pág. 918ff; H.v. Czetsch-Lindenwald, "Hilfsstoffe für Pharmazie und angrenzende Gebiete"; *Pharm. Ind.* 2, 1961, p. 72ff; Dr. H.P. Fiedler, *Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete*, Cantor KG, Aulendorf in Württemberg, 1971.

Las antiprogestinas adecuadas para los propósitos de la presente invención, preferiblemente antiprogestina (I) o un derivado o análogo de la misma aceptable para uso farmacéutico, pueden incorporarse en composiciones farmacéuticas de acuerdo con métodos conocidos para preparar composiciones medicinales para aplicación oral o parenteral, p.ej., intraperitoneal, intramuscular, subcutánea o percutánea. Pueden implantarse también en el tejido. Los implantes pueden comprender materiales inertes, p.ej., polímeros biológicamente degradables o siliconas sintéticas tales como, p.ej., goma de silicona.

Pueden administrarse bajo la forma de tabletas, píldoras, grageas, cápsulas de gel, gránulos, supositorios, implantes, soluciones, suspensiones o emulsiones acuosas u

oleosas estériles inyectables, ungüentos, cremas, geles o mediante sistemas intravaginales (p.ej., anillos vaginales) o intrauterinos (p.ej., diafragmas, rizos).

Para la preparación de un medicamento para administración oral, las antiprogestinas adecuadas para los propósitos de la presente invención que se definieron previamente pueden mezclarse con coadyuvantes o vehículos comúnmente conocidos tales como p.ej., goma arábiga, talco, almidón, azúcares tales como, p.ej., manitosa, metil celulosa, lactosa, gelatina, agentes activos en superficie, estearato de magnesio, excipientes acuosos o no acuosos, derivados de parafina, agentes reticulantes, dispersantes, emulsificadores, lubricantes, agentes conservantes y agentes saborizantes (p.ej., aceites etéreos). En una composición farmacéutica, la antiprogestina puede dispersarse en una nanopartícula, p.ej., una composición nanoparticulada.

Con el fin de mejorar la biodisponibilidad del agente activo, las antiprogestinas adecuadas para los propósitos de la presente invención que se definieron previamente pueden formularse también como clatratos de ciclodextrinas haciéndolas reaccionar con α -, β - o γ -ciclodextrinas o derivados de las mismas de acuerdo con el método que se describe en PCT/EP95/02656.

Para administración parenteral, las antiprogestinas adecuadas para los propósitos de la presente invención que

se definieron previamente pueden disolverse o suspenderse en un diluyente aceptable para el uso fisiológico tal como, p.ej., aceites con o sin solubilizadores, agentes activos en superficie, dispersantes o emulsificadores. Como aceites, p.ej. y sin limitación, puede usarse aceite de oliva, aceite de maní, aceite de semilla de algodón, aceite de soja, aceite de castor y aceite de sésamo.

La cantidad a administrar (es decir, una "cantidad efectiva para uso farmacéutico") varía dentro de un amplio rango y depende de la condición a tratar y del modo de administración. Puede cubrir cualquier cantidad suficiente para el tratamiento que se pretende. La determinación de una "cantidad efectiva para uso farmacéutico" está dentro del conocimiento de aquél entrenado en la técnica.

Una dosis unitaria puede representar entre aproximadamente 0,1 y 100 mg de agentes activos. Para una administración a humanos, la dosis diaria de agente activo es entre aproximadamente 0,1 y 400 mg, preferiblemente entre 10 y 100 mg, más preferiblemente de 50 mg.

Las composiciones farmacéuticas de acuerdo con la presente invención pueden también administrarse vía una inyección de depósito, una preparación de implante o un IUD (dispositivo intrauterino), opcionalmente para la liberación sostenida de los agentes.

El modo preferido de administración es administración

oral. Las antiprogestinas que se usan de acuerdo con la invención, y en particular, antiprogestina (I) o un derivado o análogo de la misma aceptable para uso farmacéutico, son particularmente adecuadas para administración oral.

De acuerdo con todos los aspectos de la presente invención, es también posible combinar al menos una antiprogestina como se definió previamente, en particular antiprogestina (I) o un derivado o análogo de la misma aceptable para uso farmacéutico, con al menos un antiestrógeno, ya que muchas enfermedades dependientes de hormonas, en particular cáncer de mama, muestran no solamente receptores de progesterona sino también receptores de estrógeno. El antiestrógeno puede administrarse en forma simultánea o consecutiva respecto de la antiprogestina (I) o un derivado o análogo de la misma aceptable para uso farmacéutico. La cantidad de antiprogestina y antiestrógeno puede ser igual o un componente puede ser más predominante que el otro, tal como en una relación antiprogestina: antiestrógeno ratio de 1:50 a 50:1, preferiblemente de 1:30 a 30:1, y más preferiblemente de 1:15 a 15:1.

Los ejemplos de antiestrógenos adecuados para un uso de acuerdo con la invención son antiestrógenos no esteroideos tales como tamoxifen y nafoxidina, así como raloxifen, faslodex y EM800. Los ejemplos de antiestrógenos esteroideos incluyen aquellos descritos en EP 0 348 341 A y aquellos descritos en WO 98/07740, en particular, 11β -flouro- 7α -{5-

[N-metil-N-3-(4,4,5,5,5-pentafluoropentiltio-propilamino)-pentil}-estra-1,3,5(10)-trien-3,17 β -diol, o aquellos descritos en WO 99/33855, en particular 11 β -fluoro-7 α -{5-[metil-(7,7,8,8,9,9,10,10,10-nonafluoro-decil)-amino]-pentil}-estra-1,3,5(10)-trien-3,17 β -diol, o los derivados o análogos de los mismos aceptables para uso farmacéutico. Pueden usarse también como antiestrógenos inhibidores de aromatasas que tienen un efecto antiestrogénico, tales como aquellos que se describen en las páginas 7 a 8 de EP 0 495 825 B1.

La invención se ilustra adicionalmente en los ejemplos. Los siguientes ejemplos no deben interpretarse como una limitación.

Ejemplos

Ejemplo 1:

Modelo de cáncer de mama inducido por DMBA en rata (experimento de prevención)

Materiales y Métodos:

Se usaron ratas hembras inmaduras Sprague-Dawley (49 - 51 días de edad; 10 animales/grupo) en este estudio. Se administró el carcinógeno 7,12-dimetilbenz[a]antraceno (DMBA) como una única administración oral (10 mg). Se comenzó el tratamiento 20 días después como sigue: 1) solvente control, 2) ovariectomía al inicio del tratamiento, 3) tamoxifen, 1 mg/kg s.c., 4) antiprogestina (I), 3 mg/kg, s.c., 6 días/semana. Las ratas se examinaron cada semana por palpado

de tumores de mama. Como parámetro de inhibición de crecimiento, se usó el cambio en el área tumoral (en % respecto del tamaño inicial del tumor) determinado por mediciones semanales de calibre. Para una descripción y evaluación adicional de los modelos de prevención de DMBA y NMU, véase R.G. Metha, *European Journal of Cancer* 36 (2000), páginas 1275-1282.

Resultados:

En el grupo control, todas las ratas desarrollaron tumores mamarios dentro de las 10 semanas posteriores al inicio del tratamiento (incidencia: 100%) y se observó un crecimiento progresivo del tumor. El tratamiento profiláctico con la antiprogesterina (I) previno el desarrollo de tumores por completo durante 12 semanas, y al final del experimento, después de 22 semanas, se detectó un tumor solamente en una rata (incidencia: 10%). Después de la ovariectomía al final del experimento, 40% de las ratas habían desarrollado tumores. En comparación, el tratamiento con el antiestrógeno tamoxifen redujo la incidencia de tumores solamente al 60% (véase la fig. 1)

Conclusión:

En el modelo de tumor mamario inducido por DMBA en rata, la antiprogesterina (I) suprimió completamente el desarrollo de tumores en animales intactos por más de 12 semanas después del inicio del tratamiento. La figura 1 muestra cla-

ramente la superioridad en la actividad de la antiprogestina (I) sobre el reactivo convencional contra el cáncer de mama, tamoxifen, y aún la terapia común de privación de estrógeno (ovariectomía), respecto del tratamiento profiláctico. La antiprogestina (I) es así superior a la terapia común establecida para prevenir el cáncer de mama en mujeres con alto riesgo de desarrollar la enfermedad (terapia profiláctica con tamoxifen).

Estos y los siguientes resultados indican que el uso de antiprogestina (I) para la profilaxis y el tratamiento del cáncer de mama es superior a los tratamientos comunes establecidos.

Ejemplo 2:

Modelo de cáncer de mama inducido por DMBA en rata (experimento de terapia/estudio de respuesta a la dosis)

Materiales y Métodos:

Se usaron ratas hembras inmaduras Sprague-Dawley (49 - 51 días de edad; 10 animales/grupo) en este estudio. Se indujeron tumores mamarios a través de una única administración oral de 10 mg de 7,12-dimetilbenz[a]antraceno (DMBA, Serva/Heidelberg). Las ratas con al menos un tumor establecido con un tamaño de más de 150 mm² se trataron por 4 semanas con: 1) solvente control, 2) ovariectomía al inicio del tratamiento, 3) antiprogestina (I), 0,5 mg/kg s.c., 4) antiprogestina (I), 2 mg/kg s.c., 5) antiprogestina (I), 5 mg/kg

s.c., 6) antiprogestina (I), 10 mg/kg s.c., y 7) onapristona, 5 mg/kg, s.c., diariamente. Como parámetro de inhibición de crecimiento, se usó el cambio en el área tumoral (en % respecto del tamaño inicial del tumor) determinado por mediciones semanales de calibre. Para el análisis estadístico de las diferencias entre grupos de valores medios, se usó la prueba de Kruskal-Wallis.

Resultados:

En los animales control intactos, se observó un crecimiento progresivo de los tumores, mientras que la ovariectomía causó una regresión considerable de los tumores en 90% de los animales. El tratamiento con antiprogestina (I) a dosis de 2 mg/kg o superiores resultó en una inhibición significativa del crecimiento tumoral en comparación con el control (véase la fig. 2). Existió una relación clara de dosis-respuesta. Mientras que el tratamiento con 0,5 mg/kg de antiprogestina (I) no evitó significativamente el crecimiento del tumor, a 2 mg/kg se observó una inhibición máxima del crecimiento tumoral. En este grupo, se observó una regresión completa del tumor en 50% de las ratas. El efecto de la mayor dosis de antiprogestina (I) evaluada en este experimento (10 mg/kg), fue comparable a aquél de 2 mg/kg. La onapristona (5 mg/kg, s.c.) fue notablemente menos efectiva que la antiprogestina (I) a dosis comparables.

Conclusión:

En el modelo de tumor mamario inducido por DMBA en rata, la antiprogestina (I) suprimió completamente el crecimiento tumoral en animales intactos. Se halló que la dosis de 2 mg/kg de antiprogestina (I) tiene un efecto máximo sobre el crecimiento tumoral. La antiprogestina (I) fue notablemente superior a la onapristona.

Ejemplo 3:

Modelo de cáncer de mama inducido por NMU en rata (experimento de prevención)

Materiales y Métodos:

Se indujeron tumores mediante una única inyección intravenosa de NMU (nitrosometilurea, 50 mg/kg) en ratas hembra Sprague-Dawley (obtenidas de Tierzucht Schönwalde, edad: 50-55 días). Comenzando 10 después, las ratas con al menos un tumor establecido se trataron por 4 semanas con: 1) solvente control, 2) ovariectomía al inicio del tratamiento, 3) antiprogestina (I), 1,0 mg/kg/día, 4) antiprogestina (I), 0,5 mg/kg/día y 5) onapristona, 5 mg/kg/día. Como parámetro de inhibición del crecimiento, se usó el cambio en el área tumoral (en % del tamaño inicial del tumor). Para una descripción y una evaluación adicional del modelo de prevención DMBA y NMU, véase R.G. Metha, *European Journal of Cancer* 36 (2000), páginas 1275-1282.

Resultados:

En el grupo control, todas las ratas desarrollaron tu-

mores mamarios a los 10 días después del inicio del tratamiento (incidencia: 100%; véase la fig. 3) y se observó un crecimiento tumoral progresivo. El tratamiento profiláctico con la antiprogesterona (I) previno el desarrollo tumoral completamente por 12 semanas, y al final experimento, después de 27 semanas, se detectó un tumor en solamente una rata (incidencia: 10%). En comparación, en el tratamiento con los otros antiestrógenos o el inhibidor de aromatasa letrozol, la incidencia de tumores se redujo solamente un 20 - 60%. Después de la ovariectomía al final del experimento, 20% de las ratas habían desarrollado tumores.

Conclusión:

En el modelo de tumor mamario inducido por MNU en rata, la antiprogesterona (I) suprimió completamente el desarrollo de tumores en animales intactos por más de 12 semanas después del inicio del tratamiento. El efecto del tratamiento profiláctico con antiprogesterona (I) fue superior a aquél de los antiestrógenos convencionales para la terapia de cáncer de mama (es decir, raloxifen, tamoxifen) y el inhibidor de la aromatasa letrozol y la terapia común de privación de estrógeno (ovariectomía) en lo que respecta a la incidencia y el crecimiento tumoral.

Como en el modelo de tumor inducido por DMBA (véase el Ejemplo 1), estos resultados indican que la antiprogesterona (I) previene efectivamente el desarrollo de tumores de mama

de una manera que es superior al tratamiento profiláctico normal, p.ej., con tamoxifen.

Ejemplo 4:

Modelo de cáncer de mama inducido por NMU en rata (experimento de terapia)

Materiales y Métodos:

Se indujeron tumores mediante una única inyección intravenosa de NMU (nitrosometilurea, 50 mg/kg) en ratas hembra Sprague-Dawley (obtenidas de Tierzucht Schönwalde, edad: 50-55 días). Comenzando 10 después, las ratas con al menos un tumor establecido se trataron por 4 semanas con: 1) solvente control, 2) ovariectomía al inicio del tratamiento, 3) anti-progestina (I), 1,0 mg/kg/día, 4) antiprogestina (I), 0,5 mg/kg/día y 5) onapristona, 5 mg/kg/día. Como parámetro de inhibición del crecimiento, se usó el cambio en el área tumoral (en % del tamaño inicial del tumor). Para el análisis estadístico de las diferencias entre grupos de los valores medios, se usó la prueba de Kruskal-Wallis.

Resultados:

En los animales control intactos, se observó un crecimiento progresivo de los tumores, mientras que la ovariectomía causó una inhibición completa de los tumores. El tratamiento con antiprogestina (I) a dosis de 0,5 ó 1,0 mg/kg resultó en una inhibición significativa del crecimiento del tumor en comparación con el control (véase la fig. 2). La

onapristona (5 mg/kg) fue notablemente menos efectiva que la antiprogestina (I) a la dosis mucho menor de 0,5 mg/kg.

Conclusiones:

En el modelo de tumor mamario inducido por MNU en rata, la antiprogestina (I) suprime completamente el crecimiento tumoral en animales intactos. Se halló que una dosis de 1,0 mg/kg y aún una dosis de 0,5 mg/kg de antiprogestina (I) tiene un efecto significativo sobre el crecimiento tumoral. Así, la antiprogestina (I) fue superior a antiprogestinas conocidas como la onapristona.

Ejemplo 5:

Xenoinjerto humano T47D (experimento de terapia)

Materiales y Métodos:

Se suplieron ratones hembra Fox Chase SCID (M&B) con pellets de estradiol (Innovative Research of America). Las células T47D de cáncer de mama, obtenidas de cultivos celulares y suspendidas en matrigel, se implantaron por vía s.c. en la región inguinal del ratón. El tratamiento comenzó cuando los tumores tenían aproximadamente 25 mm² de tamaño. Se continuó el tratamiento hasta que progresaran los tumores. Los grupos experimentales fueron: 1) control (vehículo), 2) ovariectomía, 3) antiprogestina (I), 10 mg/kg s.c. Se determinó el área tumoral por mediciones de calibre. Para el análisis estadístico de las diferencias entre grupos de los valores medios, se usó la prueba de Kruskal-Wallis.

Resultados:

En el modelo T47D de cáncer de mama, la ovariectomía resultó en una inhibición considerable del crecimiento de los tumores, en comparación con el crecimiento rápido del control. La figura 5 muestra que la aplicación s.c. de 10 mg/kg de antiprogestina (I) causa inhibición sobre el crecimiento tumoral. El efecto de la antiprogestina (I) es casi comparable con el efecto de la terapia convencional de privación de estrógeno (ovariectomía).

Conclusión:

El efecto de la antiprogestina (I) en la inhibición del crecimiento tumoral y, así, en la inhibición del crecimiento del cáncer de mama T47D xenoinjertado en ratones Fox Chase SCID es comparable al efecto de la terapia común de privación de estrógeno (ovariectomía), que se considera como el método más efectivo para inhibir el crecimiento de cáncer de mama en este modelo.

Ejemplo 6:

Xenoinjerto humano MCF7 (experimento de terapia)

Materiales y Métodos:

Se suplieron ratones hembra Fox Chase SCID (M&B) con pellets de estradiol (Innovative Research of America). Las células T47D de cáncer de mama, obtenidas de cultivos celulares y suspendidas en matrigel, se implantaron por vía s.c. en la región inguinal del ratón. El tratamiento comenzó

cuando los tumores tenían aproximadamente 25 mm² de tamaño. Se continuó el tratamiento hasta que progresaran los tumores. Los grupos experimentales fueron: 1) control (vehículo), 2) ovariectomía, 3) antiprogestina (I), 10 mg/kg s.c. Se determinó el área tumoral por mediciones de calibre. Para el análisis estadístico de las diferencias entre grupos de los valores medios, se usó la prueba de Kruskal-Wallis.

Resultados:

En el modelo MCF7 de cáncer de mama, la ovariectomía resultó en una inhibición considerable del crecimiento de los tumores, en comparación con el crecimiento rápido del control. La figura 6 muestra que la aplicación de 10 mg/kg de antiprogestina (I) causó también una inhibición del crecimiento tumoral, casi comparable con el efecto de la terapia convencional de privación de estrógeno (ovariectomía).

Conclusión:

El efecto de la antiprogestina (I) en la inhibición del crecimiento del cáncer de mama humano MCF7 xenoinjertado en ratones SCID Fox Chase es comparable al efecto de la terapia común de privación de estrógeno (ovariectomía), que se considera como el método más efectivo para inhibir el crecimiento de cáncer de mama en este modelo.

REIVINDICACIONES

1. Uso de la antiprogestina 11β -(4-acetilfenil)- 17β -hidroxi- 17α -(1,1,2,2,2-pentafluoroetil)-estra-4,9-dien-3-ona, o un derivado o análogo de la misma aceptable para uso farmacéutico, para la fabricación de un medicamento para la profilaxis o el tratamiento de una enfermedad dependiente de hormonas en un mamífero.

2. Un uso de acuerdo con la reivindicación 1 donde la enfermedad es cáncer de mama.

3. Un uso de acuerdo con las reivindicaciones 1 ó 2 donde el mamífero es un ser humano.

4. Un uso de acuerdo con cualquiera de las reivindicaciones precedentes donde el medicamento se administra por vía oral.

5. Un uso de acuerdo con cualquiera de las reivindicaciones precedentes donde la antiprogestina 11β -(4-acetilfenil)- 17β -hidroxi- 17α -(1,1,2,2,2-pentafluoroetil)-estra-4,9-dien-3-ona se administra en una unidad de dosificación de 50 mg.

6. Una composición farmacéutica que comprende la antiprogestina 11β -(4-acetilfenil)- 17β -hidroxi- 17α -(1,1,2,2,2-pentafluoroetil)-estra-4,9-dien-3-ona, o un derivado o análogo de la misma aceptable para uso farmacéutico, en una cantidad suficiente para la profilaxis o el tratamiento de

una enfermedad dependiente de hormonas en un mamífero.

7. Una composición farmacéutica de acuerdo con la reivindicación 6 donde la enfermedad es cáncer de mama.

8. Una composición farmacéutica de acuerdo con las reivindicaciones 6 ó 7 donde el mamífero es un ser humano.

9. Una composición farmacéutica de acuerdo con cualquiera de las reivindicaciones 6 a 8 que comprende además un antiestrógeno.

FIG. 1

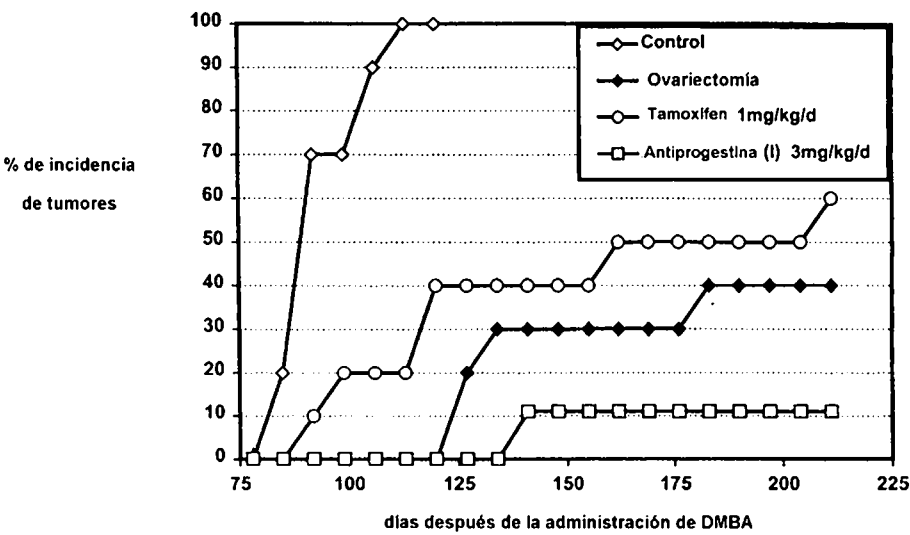


FIG. 2

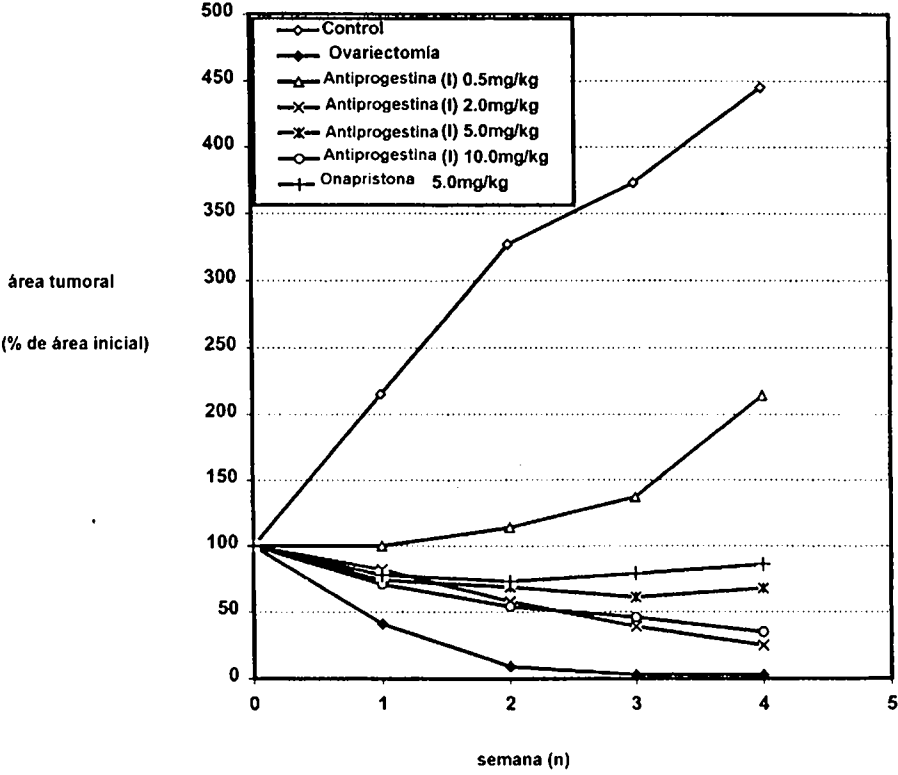


FIG. 3

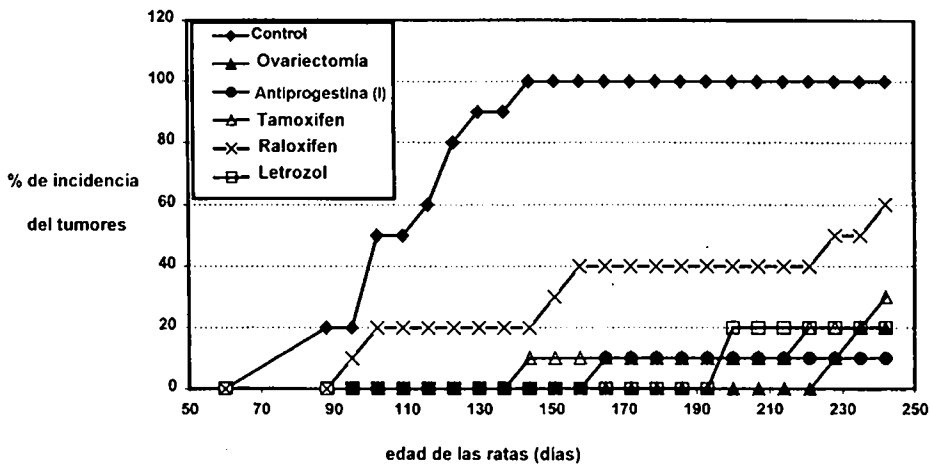


FIG. 4

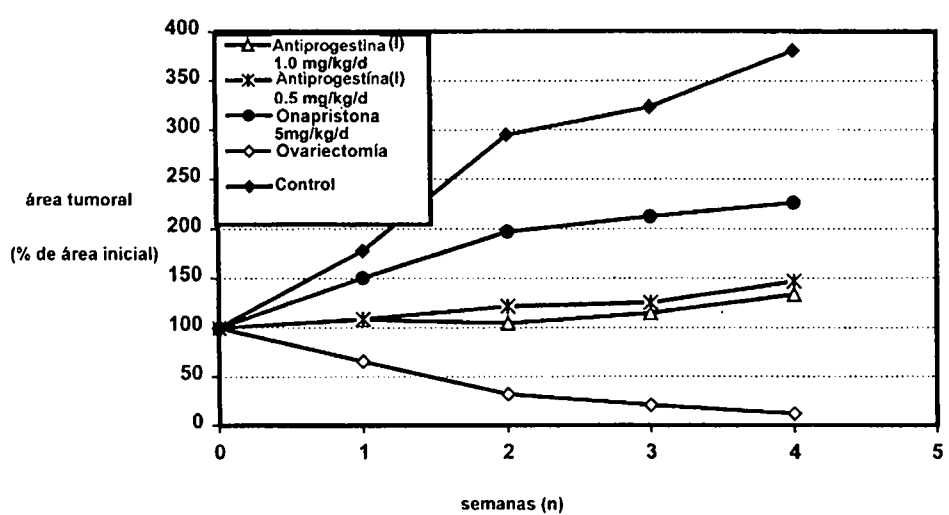


FIG. 5

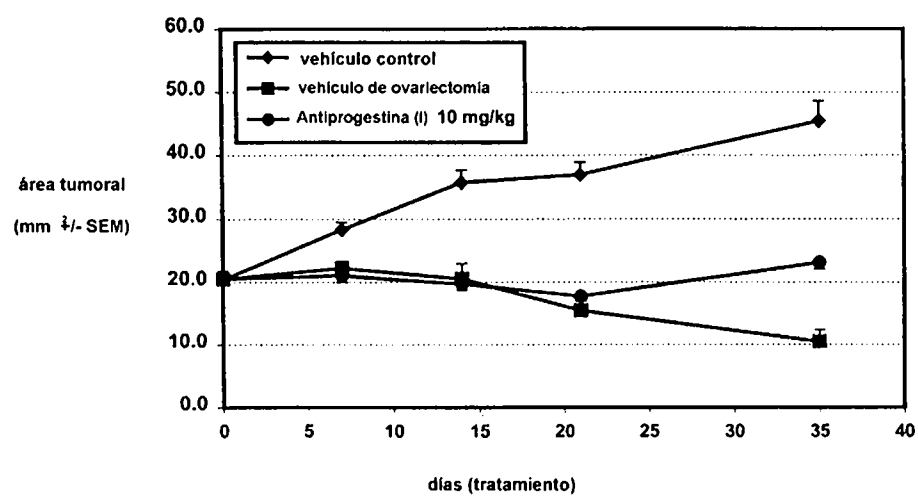
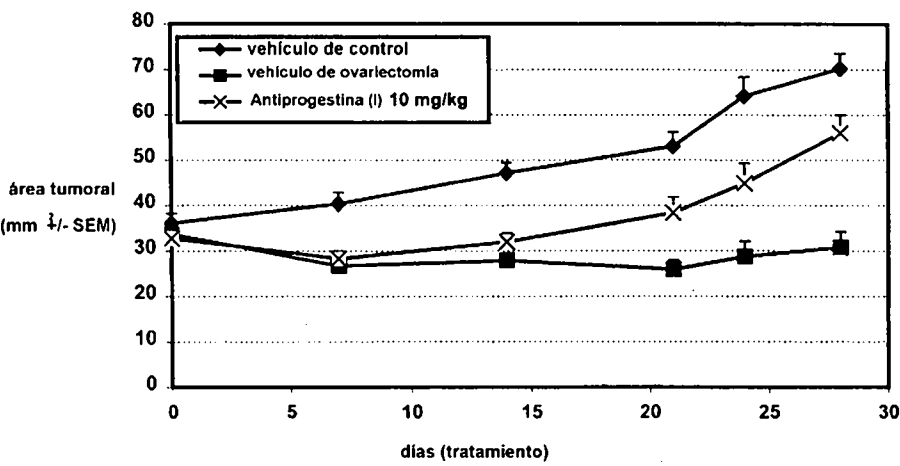


FIG. 6



PCT REQUEST

51869AWOM1XX

Original (for SUBMISSION) - printed on 17.10.2001 10:38:44 AM

0	For receiving Office use only	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	
0-4	Form - PCT/RO/101 PCT Request	
0-4-1	Prepared using	PCT-EASY Version 2.92 (updated 01.03.2001)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	European Patent Office (EPO) (RO/EP)
0-7	Applicant's or agent's file reference	51869AWOM1XX
I	Title of invention	USE OF ANTIPROGESTINS FOR PROPHYLAXIS AND TREATMENT OF HORMONE-DEPENDENT DISEASES
II	Applicant	
II-1	This person is:	applicant only
II-2	Applicant for	all designated States except US
II-4	Name	SCHERING AKTIENGESELLSCHAFT
II-5	Address:	Müllerstr. 178 D-13353 Berlin Germany
II-6	State of nationality	DE
II-7	State of residence	DE
II-8	Telephone No.	030 4681 1532
II-9	Facsimile No.	030 4681 2058
II-10	e-mail	Andreas.Broesamle@Schering.DE
III-1	Applicant and/or inventor	
III-1-1	This person is:	applicant and inventor
III-1-2	Applicant for	US only
III-1-4	Name (LAST, First)	HOFFMANN, Jens
III-1-5	Address:	Großstückenfeld 27 D-16567 Mühlenbeck Germany
III-1-6	State of nationality	DE
III-1-7	State of residence	DE

PCT REQUEST

51869AWOM1XX

Original (for SUBMISSION) - printed on 17.10.2001 10:38:44 AM

III-2	Applicant and/or inventor	
III-2-1	This person is:	applicant and inventor
III-2-2	Applicant for	US only
III-2-4	Name (LAST, First)	LICHTNER, Rosemarie
III-2-5	Address:	Belziger Str. 39 D-10823 Berlin Germany
III-2-6	State of nationality	DE
III-2-7	State of residence	DE
III-3	Applicant and/or inventor	
III-3-1	This person is:	applicant and inventor
III-3-2	Applicant for	US only
III-3-4	Name (LAST, First)	SIEMEISTER, Gerd
III-3-5	Address:	Reimerswalder Steig 26 D-13342 Berlin Germany
III-3-6	State of nationality	DE
III-3-7	State of residence	DE
III-4	Applicant and/or inventor	
III-4-1	This person is:	applicant and inventor
III-4-2	Applicant for	US only
III-4-4	Name (LAST, First)	SCHNEIDER, Martin
III-4-5	Address:	Schluchseestr. 6a D-13469 Berlin Germany
III-4-6	State of nationality	DE
III-4-7	State of residence	DE
III-5	Applicant and/or inventor	
III-5-1	This person is:	applicant and inventor
III-5-2	Applicant for	US only
III-5-4	Name (LAST, First)	FUHRMANN, Ulrike
III-5-5	Address:	Charlottenburger Ufer 6a D-10587 Berlin Germany
III-5-6	State of nationality	DE
III-5-7	State of residence	DE

PCT REQUEST

51869AWOM1XX

Original (for SUBMISSION) - printed on 17.10.2001 10:38:44 AM

IV-1	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:	common representative
IV-1-1	Name	SCHERING AKTIENGESELLSCHAFT
IV-1-2	Address:	Müllerstr. 178 D-13353 Berlin Germany
IV-1-3	Telephone No.	030 4681 1532
IV-1-4	Facsimile No.	030 4681 2058
IV-1-5	e-mail	Andreas.Broesamle@Schering.DE
V	Designation of States	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT EP: AT BE CH&LI CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE TR and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PH PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

PCT REQUEST

51869AWOM1XX

Original (for SUBMISSION) - printed on 17.10.2001 10:38:44 AM

	Accompanying items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-11	Copy of general power of attorney	✓	-
IX-17	PCT-EASY diskette	-	Diskette
IX-19	Figure of the drawings which should accompany the abstract		
IX-20	Language of filing of the international application	English	
X-1	Signature of applicant, agent or common representative	<i>A. Brös - G</i>	
X-1-1	Name	SCHERING AKTIENGESELLSCHAFT	
X-1-2	Name of signatory	i.V. Dr. Brösamle	
X-2	Signature of applicant, agent or common representative	<i>S. Kurilla</i>	
X-2-1	Name	SCHERING AKTIENGESELLSCHAFT	
X-2-2	Name of signatory	i.A. S. Kurilla	

FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	
10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/EP
10-6	Transmittal of search copy delayed until search fee is paid	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	
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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 51869AWOM1XX	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP01/12005	International filing date (day/month/year) 17/10/2001	Priority date (day/month/year) 18/10/2000
International Patent Classification (IPC) or national classification and IPC A61K31/56		
Applicant SCHERING AKTIENGESELLSCHAFT et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

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

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 03/04/2002	Date of completion of this report 23.01.2003
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Domingues, H Telephone No. +49 89 2399 7810 

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP01/12005

I. Basis of the report

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

Description, pages:

1-18 as originally filed

Claims, No.:

1-9 as originally filed

Drawings, sheets:

1-6 as originally filed

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

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

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

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

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

4. The amendments have resulted in the cancellation of:

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

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP01/12005

☐ the drawings, sheets:

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

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

6. Additional observations, if necessary:

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

1. Statement

Novelty (N)	Yes: Claims 2
	No: Claims 1, 3-9

Inventive step (IS)	Yes: Claims 2
	No: Claims

Industrial applicability (IA)	Yes: Claims 1-9
	No: Claims

2. Citations and explanations see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP01/12005

Concerning section V

1. This opinion is based on the following documents cited in the international search report:

D1: DE 197 06 061 A (SCHERING AG) 13 August 1998 (1998-08-13)

D2: FUHRMANN ULRIKE ET AL.: 'Synthesis and Biological Activity of a Novel, Highly Potent Progesterone Receptor Antagonist' JOURNAL OF MEDICINAL CHEMISTRY., vol. 43, no. 26, 7 December 2000 (2000-12-07), pages 5010-5016, XP001064233 AMERICAN CHEMICAL SOCIETY, WASHINGTON., US ISSN: 0022-2623.*

* Since the present application claims a valid priority date (18.10.00), this document will not be regarded as relevant during the regional phase.

2. Clarity, Art. 6 PCT

Claim 1 lacks clarity because the therapeutic indication is defined in functional terms - *treatment of a hormone-dependent disease*. Since this functional definition encompasses a vast number of diseases ranging from breast cancer to premenstrual syndrome and post-natal depression, the skilled man would know which of those diseases are actually covered by the scope of the claim. Support could only be found for a limited number of hormone-dependent diseases (see pg. 7, lines 13-16).

3. Novelty (Art. 33(2) PCT) and inventive step (Art. 33(3) PCT)

D1 discloses the use of antiprogestins, including the antiprogestin referred to in claim 1 (antiprogestin (I)) for the treatment of hormonal abnormalities, dysmenorrhoea, endometriosis, myoma and hormone-dependent carcinoma (see pg. 3, line 30, pg. 4, lines 52-57 and 64). The use of said antiprogestins in combination with antiestrogens for the treatment of hormone-dependent tumors, gynaecological disorders and for the induction of labour is also disclosed (pg. 4, lines 58-61). Compositions comprising antiprogestins, such as antiprogestin (I) alone or in combination with antiestrogens are said to be obtainable by methods known in the art. The compositions may be formulated as tablets or capsules and may contain between 0.1-100 mg of active compound (pg. 5, lines 30-47). Therefore, D1 is novelty destroying for **claims 1, 3-5**. Furthermore, since compositions comprising antiprogestin (I), alone in combination with antiestrogens are known from D1, the intended use specified in **claims 6-9** does not render these claims novel.

INTERNATIONAL PRELIMINARY

International application No. PCT/EP01/12005

EXAMINATION REPORT - SEPARATE SHEET

The use of progestin (I) for the treatment of breast cancer does not appear to have been explicitly disclosed or suggested in D1. Therefore, claims 2 appears to be novel and inventive.

Tratado de Cooperación en Materia de Patentes

Informe de Examen Preliminar Internacional

(Artículo PCT 36 y Regla 70)

Referencia del solicitante o agente: 51869QWOM1XX

Para acción futura: Véase la Notificación de Comunicación del Informe de Examen Preliminar Internacional (Formulario PCT/IPEA/416)

Solicitud Internacional No. PCT/EP01/12005

Fecha de presentación internacional: 17/10/2001

Fecha de Prioridad: 18/10/2000

Clasificación Internacional de Patentes (IPC) o clasificación nacional e IPC: A61K31/56

Solicitante: Schering Aktiengesellschaft y otros

1. Este Informe de Examen Preliminar Internacional ha sido preparado por esta Autoridad de Examen Preliminar Internacional y es comunicado al solicitante de acuerdo con el Artículo 36.
2. Este Informe consiste de un total de 5 hojas, incluyendo esta carátula

Este informe también es acompañado de anexos, p. ej. hojas con la descripción, reivindicaciones y/o dibujos que han sido corregidos y que son la base para este informe y/o hojas que contienen rectificaciones hechas ante esta Autoridad (véase Regla 70.16 y Sección 607 de las Instrucciones Administrativas bajo el PCT).

Estos anexos consisten de un total de hojas.

3. Este informe contiene indicaciones en relación con los siguientes items:

I (X) Base del informe

II Prioridad

III No-establece opinión en relación con la novedad, altura inventiva y aplicabilidad industrial

IV Falta de unidad inventiva

V (X) Declaración razonada bajo el Artículo 35(2) en relación con la novedad, altura inventiva o aplicabilidad industrial; citas y explicaciones que sustentan tal declaración

VI Ciertos documentos citados

VII Ciertos defectos en la solicitud internacional

VIII Ciertas observaciones con respecto a la solicitud internacional.

Fecha de comunicación de la solicitud: 03/04/2002

Fecha de terminación de este informe: 23.01.2003

Informe de Examen preliminar Internacional

Solicitud internacional No. PCT/EP01/12005

I. Base del Informe

1. Con respecto a los elementos de la solicitud internacional (hojas de reemplazo que han sido provistas a la oficina receptora en respuesta a una invitación bajo Artículo 14 son mencionadas en este informe como "originalmente presentadas" y no están adjuntas a este informe ya que no contienen modificaciones (Reglas 70.16 y 70.17))

Descripción, hojas

1-18 como originalmente presentadas

Reivindicación, No.

1-9 como originalmente presentadas

Dibujos, hojas

1-6 como originalmente presentadas

2. Con respecto al idioma, todos los elementos indicados más arriba estaban disponibles o fueron provistos a esta Autoridad en el idioma en el cual fue presentada la solicitud internacional, a menos que esté indicado bajo este ítem.

Estos elementos estaban disponibles o fueron provistos a esta Autoridad en el siguiente idioma: , que es:

El idioma de una traducción provista a los fines de la búsqueda internacional (bajo Regla 23.1(b)).

El idioma de la publicación de la solicitud internacional (bajo Regla 48.3(b)).

El idioma de una traducción provista a los fines del examen preliminar internacional (bajo Regla 55.2 y/o 55.3).

3. Con respecto a cualquier nucleótido y/o secuencia de aminoácidos divulgada en la solicitud internacional, el examen preliminar internacional fue llevado a cabo sobre la base de los listados de secuencias:

Contenido en forma escrita en la solicitud internacional

Presentado junto con la solicitud internacional en una forma descifrable por computadora

Provista subsecuentemente a esta Autoridad en forma escrita

Provista subsecuentemente a esta Autoridad en una forma descifrable por computadora

La declaración de que el listado de secuencias provisto subsecuentemente no va más allá de lo divulgado en la solicitud internacional tal como fuera presentada

La declaración de que ha sido provista la información grabada en forma descifrable por computadora es idéntica al listado de secuencias escrito

4. Las correcciones han dado como resultado la cancelación de la descripción, páginas:

las reivindicación, Nos.:

los dibujos, hojas:

5. Este informe fue emitido como si (algunas de) las correcciones no hubieran sido hechas, porque han sido consideradas como que van más allá de la divulgación tal cual fue presentada (Regla 70.2(C):

(Cualquier hoja de reemplazo que contenga este tipo de correcciones debe ser mencionada bajo el ítem 1 y anexada a este informe.)

6. Observaciones adicionales, de ser necesario:

V. Declaración razonada bajo Artículo 35(2) con respecto a novedad, altura inventiva y aplicación industrial, citas y explicaciones que avalen dicha declaración

1. Declaración

Novedad (N) Si: Reivindicación 2

No: Reivindicación 1, 3-9

Altura Inventiva (IS) Si: Reivindicación 2

No: Reivindicaciones

Aplicación Industrial (IA) Si: reivindicaciones 1-9

No: reivindicaciones

2. Citas y explicaciones

ver hoja aparte

Informe de Examen Preliminar Internacional

Hoja separada

Solicitud internacional No. PCT/EP01/12005

En relación con la Sección V

1. Esta opinión está basada en los siguientes documentos citados en el informe de búsqueda internacional:

D1: DE 197 06 061 A (Schering AG) 13 de agosto de 1998 (1998-08-13)

D2: Fuhrmann Ulrike y otros: "Synthesis and Biological Activity of a Novel Highly Potent Progesterone Receptor Antagonist" Journal of Medicinal Chemistri, vol. 43, No. 26, 7 de diciembre de 2000 (2000-12-07), pág. 5010-5016, XP001064233 American Chemical Society. Washington, US ISSN: 022-2523*

- Debido a que la presente solicitud reivindica una fecha válida de prioridad (18.10.00= este documento no será considerado relevante durante la fase regional.

3. Claridad, Art. 6 PCT

Reivindicación 1 carece de claridad debido a que la indicación terapéutica es definida en términos funcionales -tratamiento de una enfermedad hormona-dependiente. Debido a que esta definición funcional abarca un vasto número de enfermedades que van desde el cáncer de mama al síndrome premenstrual y la depresión post-parto, el técnico versado en la material querría saber cuál de esas enfermedades están realmente cubiertas por el alcance de la reivindicación. Se pudo encontrar el aval solo para un número

limitado de enfermedades hormona-dependientes (ver pág. 7, líneas 13-16).

3. Novedad (Art. 33(2) PCT) y altura inventiva (Art. 33(3)PCT)

D1 describe el uso de antiprogestinas, incluyendo la antiprogestina mencionada en la reivindicación 1 (antiprogestina (I)) para el tratamiento de anormalidades hormonales, dismenorreas, endometriosis, mioma y carcinoma hormona-dependiente (ver pág. 3, línea 30, pág. 4, líneas 52-57 y 64) El uso de dicha antiprogestinas en combinación con antiestrógeno para el tratamiento de tumores hormona-dependientes, desórdenes ginecológicos y para la inducción del parto también son descriptos (pág. 4, líneas 58-61). Es sabido que composiciones que contienen antiprogestinas, tales como antiprogestina (I) sola o en combinación con antiestrógenos son obtenibles mediante métodos conocidos en el arte. Las composiciones pueden ser formuladas como pastillas o cápsulas y pueden contener entre 0.1-100mg de principio activo (pág. 5, líneas 30-47). En consecuencia, D1 afecta la novedad de las reivindicaciones 1, 3-5. Además, debido a que de D1 son conocidas las composiciones que comprenden antiprogestina (I), sólo en combinación con antiestrógenos, el uso previsto, especificado en las reivindicaciones 6-9 no le aporta novedad a estas reivindicaciones. El uso de progestina (I) para el tratamiento de cáncer de mama no aparenta haber sido descrito explícitamente o sugerido en D1. Por lo tanto, la reivindicación 2 aparenta ser novedosa e inventiva.

PATENT COOPERATION TREATY

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PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

From the INTERNATIONAL BUREAU

To:

SCHERING AKTIENGESELLSCHAFT
Müllerstr. 178
13353 Berlin
ALLEMAGNE

Date of mailing (day/month/year) 11 February 2002 (11.02.02)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference 51869AWOM1XX	
International application No. PCT/EP01/12005	
International publication date (day/month/year) Not yet published	
Applicant SCHERING AKTIENGESELLSCHAFT et al	International filing date (day/month/year) 17 October 2001 (17.10.01) Priority date (day/month/year) 18 October 2000 (18.10.00)

- The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
- This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
- An asterisk (*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
- The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, **the attention of the applicant is directed** to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

<u>Priority date</u>	<u>Priority application No.</u>	<u>Country or regional Office or PCT receiving Office</u>	<u>Date of receipt of priority document</u>
18 Octo 2000 (18.10.00)	00250341.5	EP	30 Janu 2002 (30.01.02)
18 Octo 2000 (18.10.00)	60/240,998	US	NR

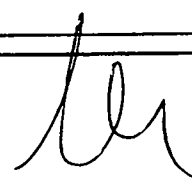
The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

N. Wagner

Telephone No. (41-22) 338.83.38



004653503

PATENT COOPERATION TREATY

PCT

NOTIFICATION CONCERNING
SUBMISSION OR TRANSMITTAL
OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

From the INTERNATIONAL BUREAU

To:

SCHERING AKTIENGESELLSCHAFT
Müllerstr. 178
13353 Berlin
ALLEMAGNE

AB

ON

Br

Date of mailing (day/month/year) 27 March 2002 (27.03.02)	
Applicant's or agent's file reference 51869AWOM1XX00 + P	IMPORTANT NOTIFICATION
International application No. PCT/EP01/12005 ✓	International filing date (day/month/year) 17 October 2001 (17.10.01) ✓
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 18 October 2000 (18.10.00)
Applicant SCHERING AKTIENGESELLSCHAFT et al	

- The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
- This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
- An asterisk (*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
- The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

<u>Priority date</u>	<u>Priority application No.</u>	<u>Country or regional Office or PCT receiving Office</u>	<u>Date of receipt of priority document</u>
18 Octo 2000 (18.10.00)	00250341.5	EP	30 Janu 2002 (30.01.02)
18 Octo 2000 (18.10.00)	60/240,998	US	19 Marc 2002 (19.03.02)

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

Somsak THIPHRAKESONE

Telephone No. (41-22) 338.83.38

004749906

PATENT COOPERATION TREATY

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PCT

NOTICE INFORMING THE APPLICANT OF THE
COMMUNICATION OF THE INTERNATIONAL
APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

From the INTERNATIONAL BUREAU

To:
SCHERING AKTIENGESELLSCHAFT
Müllerstr. 178
13353 Berlin
ALLEMAGNEAB
ON

Rn

14

Date of mailing (day/month/year)

25 April 2002 (25.04.02)

Applicant's or agent's file reference

51869AWOM1XX 00 + P

IMPORTANT NOTICE

International application No.

PCT/EP01/12005

International filing date (day/month/year)

17 October 2001 (17.10.01)

Priority date (day/month/year)

18 October 2000 (18.10.00)

Applicant

SCHERING AKTIENGESELLSCHAFT et al

1. Notice is hereby given that the International Bureau has **communicated**, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this notice:

KP, KR, US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

AE, AG, AL, AM, AP, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EA, EC, EE, EP, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OA, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA,

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this notice is a copy of the international application as published by the International Bureau on 25 April 2002 (25.04.02) under No. WO 02/32430

4. **TIME LIMITS for filing a demand for international preliminary examination and for entry into national phase**

The applicable time limit for entering the national phase will, **subject to what is said in the following paragraph** be **30 MONTHS** from the priority date, not only in respect of any elected Office if a demand for international preliminary examination is filed before the expiration of **19 months** from the priority date, but also in respect of any designated Office, in the absence of filing of such demand, where Article 22(1) as modified with effect from 1 April 2002 applies in respect of the designated Office. For further details, see PCT Gazette No. 44/2001 of 1 November 2001, pages 19926, 19932 and 19934, as well as the PCT Newsletter, October and November 2001 and February 2002 issues.

In practice, **time limits other than the 30-month time limit** will continue to apply, for various periods of time, in respect of certain designated or elected Offices. For **regular updates on the applicable time limits** (20, 21, 30 or 31 months, or other time limit), Office by Office, refer to the PCT Gazette, the PCT Newsletter and the PCT Applicant's Guide, Volume II, National Chapters, all available from WIPO's Internet site, at <http://www.wipo.int/pct/en/index.html>.

For filing a **demand for international preliminary examination**, see the PCT Applicant's Guide, Volume I/A, Chapter IX. Only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II.)

It is the applicant's **sole responsibility** to monitor all these limits.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer

J. Zahra

Telephone No. (41-22) 338.91.11

133

Continuation of Form PCT/IB/308

**NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF
THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES**

Date of mailing (day/month/year) 25 April 2002 (25.04.02)	IMPORTANT NOTICE
Applicant's or agent's file reference 51869AWOM1XX 00+P	International application No. PCT/EP01/12005
The applicant is hereby notified that, at the time of establishment of this Notice, the time limit under Rule 46.1 for making amendments under Article 19 has not yet expired and the International Bureau had received neither such amendments nor a declaration that the applicant does not wish to make amendments.	

PATENT COOPERATION TREATY

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PCT

NOTIFICATION OF RECEIPT OF
RECORD COPY

(PCT Rule 24.2(a))

From the INTERNATIONAL BUREAU

To:

SCHERING AKTIENGESELLSCHAFT
Müllerstr. 178
13353 Berlin
ALLEMAGNEHB
ON Br h

Date of mailing (day/month/year) 07 January 2002 (07.01.02)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference 51869AWOM1XX00 +P	International application No. PCT/EP01/12005 ✓

The applicant is hereby notified that the International Bureau has received the record copy of the international application as detailed below.

Name(s) of the applicant(s) and State(s) for which they are applicants:

SCHERING AKTIENGESELLSCHAFT (for all designated States except US)
HOFFMANN, Jens et al (for US)

International filing date

17 October 2001 (17.10.01) ✓

Priority date(s) claimed

18 October 2000 (18.10.00)

18 October 2000 (18.10.00)

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

21 December 2001 (21.12.01)

List of designated Offices:

AP : GH,GM,KE,LS,MW,MZ,SD,SL,SZ,TZ,UG,ZW
EA : AM,AZ,BY,KG,KZ,MD,RU,TJ,TM
EP : AT,BE,CH,CY,DE,DK,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE,TR
OA : BF,BJ,CF,CG,CI,CM,GA,GN,GQ,GW,ML,MR,NE,SN,TD,TG
National : AE,AG,AL,AM,AT,AU,AZ,BA,BB,BG,BR,BY,BZ,CA,CH,CN,CO,CR,CU,CZ,DE,DK,DM,DZ,
EC,EE,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KP,KR,KZ,LC,LK,LR,LS,LT,LU,
LV,MA,MD,MG,MK,MN,MW,MX,MZ,NO,NZ,PH,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,TZ,
UA,UG,US,UZ,VN,YU,ZA,ZW

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer: N. Wagner
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.83.38

Continuation of Form PCT/IB/301

NOTIFICATION OF RECEIPT OF RECORD COPY

137

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Date of mailing (day/month/year) 07 January 2002 (07.01.02)	IMPORTANT NOTIFICATION
Applicant's or agent's file reference 51869AWOM1XX	International application No. PCT/EP01/12005

ATTENTION

The applicant should carefully check the data appearing in this Notification. In case of any discrepancy between these data and the indications in the international application, the applicant should immediately inform the International Bureau.

In addition, the applicant's attention is drawn to the information contained in the Annex, relating to:

- ☒ time limits for entry into the national phase
- ☐ confirmation of precautionary designations
- ☒ requirements regarding priority documents

A copy of this Notification is being sent to the receiving Office and to the International Searching Authority.

INFORMATION ON TIME LIMITS FOR ENTERING THE NATIONAL PHASE

The applicant is reminded that the "national phase" must be entered before each of the designated Offices indicated in the Notification of Receipt of Record Copy (Form PCT/IB/301) by paying national fees and furnishing translations, as prescribed by the applicable national laws.

The time limit for performing these procedural acts is **20 MONTHS** from the priority date or, for those designated States which the applicant elects in a demand for international preliminary examination or in a later election, **30 MONTHS** from the priority date, provided that the election is made before the expiration of 19 months from the priority date. Some designated (or elected) Offices have fixed time limits which expire even later than 20 or 30 months from the priority date. In other Offices an extension of time or grace period, in some cases upon payment of an additional fee, is available.

In addition to these procedural acts, the applicant may also have to comply with other special requirements applicable in certain Offices. **It is the applicant's responsibility** to ensure that the necessary steps to enter the national phase are taken in a timely fashion. Most designated Offices do not issue reminders to applicants in connection with the entry into the national phase.

For detailed information about the procedural acts to be performed to enter the national phase before each designated Office, the applicable time limits and possible extensions of time or grace periods, and any other requirements, see the relevant Chapters of Volume II of the PCT Applicant's Guide. Information about the requirements for filing a demand for international preliminary examination is set out in Chapter IX of Volume I of the PCT Applicant's Guide.

GR and ES became bound by PCT Chapter II on 7 September 1996 and 6 September 1997, respectively, and may, therefore, be elected in a demand or a later election filed on or after 7 September 1996 and 6 September 1997, respectively, regardless of the filing date of the international application. (See second paragraph above.)

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

CONFIRMATION OF PRECAUTIONARY DESIGNATIONS

This notification lists only specific designations made under Rule 4.9(a) in the request. It is important to check that these designations are correct. Errors in designations can be corrected where precautionary designations have been made under Rule 4.9(b). The applicant is hereby reminded that any precautionary designations may be confirmed according to Rule 4.9(c) before the expiration of 15 months from the priority date. If it is not confirmed, it will automatically be regarded as withdrawn by the applicant. There will be no reminder and no invitation. Confirmation of a designation consists of the filing of a notice specifying the designated State concerned (with an indication of the kind of protection or treatment desired) and the payment of the designation and confirmation fees. Confirmation must reach the receiving Office within the 15-month time limit.

REQUIREMENTS REGARDING PRIORITY DOCUMENTS

For applicants who have not yet complied with the requirements regarding priority documents, the following is recalled.

Where the priority of an earlier national, regional or international application is claimed, the applicant must submit a copy of the said earlier application, certified by the authority with which it was filed ("the priority document") to the receiving Office (which will transmit it to the International Bureau) or directly to the International Bureau, before the expiration of 16 months from the priority date, provided that any such priority document may still be submitted to the International Bureau before that date of international publication of the international application, in which case that document will be considered to have been received by the International Bureau on the last day of the 16-month time limit (Rule 17.1(a)).

Where the priority document is issued by the receiving Office, the applicant may, instead of submitting the priority document, request the receiving Office to prepare and transmit the priority document to the International Bureau. Such request must be made before the expiration of the 16-month time limit and may be subjected by the receiving Office to the payment of a fee (Rule 17.1(b)).

If the priority document concerned is not submitted to the International Bureau or if the request to the receiving Office to prepare and transmit the priority document has not been made (and the corresponding fee, if any, paid) within the applicable time limit indicated under the preceding paragraphs, any designated State may disregard the priority claim, provided that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity to furnish the priority document within a time limit which is reasonable under the circumstances.

Where several priorities are claimed, the priority date to be considered for the purposes of computing the 16-month time limit is the filing date of the earliest application whose priority is claimed.

PATENT COOPERATION TREATY

13-9

PCT

NOTIFICATION OF THE RECORDING
OF A CHANGE(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

SCHERING AKTIENGESELLSCHAFT
Müllerstr. 178
13353 Berlin
ALLEMAGNE

Patente

19. Feb. 2002

Frist:

Date of mailing (day/month/year)
13 February 2002 (13.02.02)Applicant's or agent's file reference
51869AWOM1XXOO+P

IMPORTANT NOTIFICATION

International application No.
PCT/EP01/12005✓International filing date (day/month/year)
17 October 2001 (17.10.01)✓

1. The following indications appeared on record concerning:

☒ the applicant ☒ the inventor ☐ the agent ☐ the common representative

Name and Address

SIEMEISTER, Gerd
Reimerswalder Steig 26
13342 Berlin
GermanyState of Nationality
DEState of Residence
DE

Telephone No.

Facsimile No.

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☒ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address

SIEMEISTER, Gerhard
Reimerswalder Steig 26
13503 Berlin
GermanyState of Nationality
DEState of Residence
DE

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office ☐ the designated Offices concerned
☒ the International Searching Authority ☐ the elected Offices concerned
☐ the International Preliminary Examining Authority ☐ other:The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

N. Wagner

Facsimile No.: (41-22) 740.14.35

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

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To:

SCHERING AKTIENGESELLSCHAFT

Müllerstr. 178
13353 Berlin
ALLEMAGNE

Patente *Be*

02. Mai 2002 *h*

Frist: 29.06.

Patent. of

WRITTEN OPINION

(PCT Rule 66)

Date of mailing
(day/month/year) 29/04/2002

Applicant's or agent's file reference

51869AWOM1XXOO + P

REPLY DUE

within 2 / 00 months/days
from the above date of mailing

International application No.

PCT/EP 01/12005 ✓

International filing date (day/month/year)

17/10/2001

Priority date (day/month/year)

18/10/2000

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

A61K31/56

Applicant

SCHERING AKTIENGESELLSCHAFT et al.

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

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

I ☒ Basis of the opinion

II ☐ Priority

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

IV ☐ Lack of unity of invention

V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

VI ☐ Certain documents cited

VII ☐ Certain defects in the international application

VIII ☐ Certain observations on the international application

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

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

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

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

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

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

18/02/2003

Name and mailing address of the IPEA/



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

Authorized officer

Examiner

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



WRITTEN OPINION

International application No PCT/EP 01/12005

I. Basis of the opinion

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

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

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

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

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

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

3. If amendments are filed, the applicant should comply with the requirements of Rule 66.8 PCT and indicate the basis of the amendments in the documents of the application as originally filed (Article 34 (2) (b) PCT) otherwise these amendments may not be taken into consideration for the establishment of the international preliminary examination report. The attention of the applicant is drawn to the fact that if the application contains an unnecessary plurality of independent claims, no examination of any of the claims will be carried out.

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

Tratado de Cooperación en Materia de Patentes

De la Autoridad de Examen Preliminar Internacional

A: Schering Aktiengesellschaft, Müllerstrasse 178, 13353 Berlin, Alemania.

OPINION ESCRITA

Fecha de envío: 29/04/2002

Referencia del solicitante o agente: 51869AWOM1XX00+P

Plazo para responder: dentro de los 2 meses desde la fecha de envío mencionada.

Solicitud Internacional No. PCT/EP 01/12005

Fecha de presentación internacional: 17/10/2001

Fecha de Prioridad: 18/10/2000

Clasificación Internacional de Patentes (IPC) o clasificación nacional e IPC: A61K31/59

Solicitante: Schering Aktiengesellschaft y otros

1. Esta opinión escrita es la primera emitida por esta Autoridad de Examen Preliminar Internacional

2. Esta opinión contiene indicaciones relacionadas con los siguientes puntos:

I Base de la opinión

II Prioridad

III No emisión de opinión con respecto a la novedad, altura inventiva y aplicación industrial

IV Falta de unidad inventiva

V(X) Declaración razonada bajo Regla 66.2 (a)(ii) con respecto a novedad, altura inventiva o aplicación industrial; citas y explicaciones que apoyan tal declaración.

VI Ciertos documentos citados

VII Ciertos defectos de la solicitud internacional

VIII Ciertas observaciones con respecto a la solicitud internacional

3. Se invita por la presente al solicitante a responder a esta opinión.

Cuándo? Véase el límite de tiempo indicado más arriba. El solicitante puede, antes del vencimiento del límite de tiempo, solicitar una prórroga a esta Autoridad (ver Regla 66.2(d)).

Cómo? Enviando una contestación escrita, acompañada, si fuera apropiado, por correcciones, de acuerdo con la Regla 66.3. Para la forma y el idioma de las correcciones, ver reglas 66.8 y 66.9.

También Para una oportunidad adicional de presentar correcciones, ver Regla 66.4. Para la obligación del examinador de tomar en consideración correcciones y/o argumentos, ver Regla 66.4bis. Para una comunicación informal con el examinador, ver Regla 66.6.

Si no se presenta una contestación, el informe de examen preliminar internacional será establecido sobre la base de esta opinión.

4. La fecha límite en que el informe de examen preliminar internacional debe ser establecido, de acuerdo con la Regla 69.2, es el: 18/02/2003

OPINIÓN ESCRITA

I. Base de la opinión

Esta opinión escrita se basa en la solicitud como fue presentada originalmente

III. No-establece opinión en relación a la novedad, altura inventiva y aplicación industrial

La pregunta de si la invención reivindicada presenta novedad, altura inventiva o es industrialmente aplicable no ha sido y no será objeto del examen preliminar internacional con respecto a las reivindicaciones, las cuales aún no han sido sometidas a la búsqueda (Artículo 17(2) (a) o (3) y Regla 66.1(e) PCT: vease también el informe de búsqueda internacional.

V. Declaración razonada bajo Regla 66.2(a)(ii) con respecto a novedad, altura inventiva o aplicación industrial

1. Hasta el punto en que el examen preliminar internacional ha sido llevado a cabo (véase ítem III más arriba), se puntualiza lo siguiente:

2. En vista de los documentos citados en el informe de búsqueda internacional, se considera que la invención, como es definida en al menos algunas de las reivindicaciones, que han sido objeto de un informe de búsqueda internacional, no parece alcanzar el criterio mencionado en el Artículo 33(1)PCT, es decir que no parece ser nueva

y/o tener altura inventiva (ver el informe de búsqueda internacional, en particular los documentos citados con X y/o Y y las correspondientes referencias a las reivindicaciones.

3. Si se presentan correcciones, el solicitante debería cumplimentar los requisitos de la Regla 66.8PCT e indicar la base de las correcciones en los documentos de la solicitud como fue presentada originalmente (Artículo 34 (2) (b) PCT) de otro modo estas correcciones pueden no ser tenidas en cuenta para la confección del informe de examen preliminar internacional. Se llama la atención del solicitante sobre el hecho de que si la solicitud contiene una pluralidad innecesaria de reivindicaciones independientes, no se llevará a cabo el examen de ninguna de estas reivindicaciones.

Nota: Si el solicitante decidiera solicitar un examen de fondo detallado, entonces normalmente se establecerá directamente un informe de examen preliminar internacional. Excepcionalmente el examinador puede emitir una segunda opinión escrita, si esto fuera solicitado explícitamente.

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EUROPÄISCHES PATENTAMT

ERHARDTSTRASSE 27
D-80298 MÜNCHEN

Schering AG
Corporate Patents

By Telefax
comp. copy 2 ps.

Your Ref.	Your letter dated	Our Ref. (please indicate when replying)	Telephone: +49-30- 468-11532 +49-30- 4 68-11 11	Date
	29-04-02	ab-ku	Telefax: +49-30- 468-12058	2002-06-26

International Application No. PCT/EP01/12005
Applicant: Schering Aktiengesellschaft
Our Ref: 51869AWOM1XX00+P

Response to the Written Opinion according to Rule 66

The applicant would like to provide the following comments in response to the Written Opinion of April 29, 2002:

Basis of the Opinion (Item III)

The standard language regarding non-establishment of an opinion with respect to certain subject matter appears in Item III of the Written Opinion. In this regard, the Applicant notes that the International Search Report mailed 21 March 2002 does not indicate that any subject matter was not searched. Indeed, the report is based on the subject matter of claims 1 – 9, as the "P" document is cited als relevant for these claims. Accordingly, the question of whether the claimed invention appears to be novel, to involve an inventive step or be industrially applicable should be addressed in the International Preliminary Examination Report for the entire claimed subject matter, specifically, claims 1 – 9.

Reasoned Statement with regard to Novelty, Inventive Step or Industrial Applicability (Item V)

The Written Opinion states that the invention, at least as defined in some of the claims, does not appear to be novel or inventive in view of the International Search Report and the subject matter searched therein.

Address

European Patent Office

Our Ref.

ab-ku

Date

2002-06-26

Page

2

The International Search Report cited one "X" document, DE 197 06 061 A. This document, however, is only stated as relevant for claims 1, 3 – 6, 8 and 9, so that the subject matter of at least claims 2 and 7 should be acknowledged as novel and inventive. As to the subject matter of claims 1, 3 – 6, 8 and 9, the cited document merely discloses that compounds of a general formula may be suitable for several indications. The predominant indication is contraception and post-coital fertility control (see page 4, lines 47 – 51). Other mentioned indications are treating hormonal abnormalities, including menstruation or childbirth, hormone-replacement therapy and treating dysmenorrhea, endometriosis and hormone-dependent cancer (page 4, lines 52 – 57). Yet, it is not disclosed that the specific compound 11 β -(4-acetylphenyl)-17 β -hydroxy-17 α -(1,1,2,2,2-pentafluoroethyl)-estra-4,9-dien-3-one may be used for the treatment or prophylaxis of a hormone-dependent disease. The application for the first time discloses this specific use for the particular compound, and moreover, provides strong evidence in standard animal models that 11 β -(4-acetylphenyl)-17 β -hydroxy-17 α -(1,1,2,2,2-pentafluoroethyl)estra-4,9-dien-3-one may be used for both the treatment and prophylaxis of a hormone-dependent disease, for example, breast cancer. Accordingly, the subject matter of claim 1, as well as the subject matter of its dependent claims 2 – 9, should be considered novel and inventive over the cited "X" document.

Finally, the "P" document cited in the International Search Report has no relevance to the present application. As the text of the International Application is basically identical to the text of the priority documents the subject matter of the invention is entitled to the priority date of 18 October 2000. Thus, the document published in December 2000 is not prior art.

The applicant herewith asks for a substantive International Preliminary Examination Report, considering the afore mentioned arguments.

SCHERING AKTIENGESELLSCHAFT

i.V.



Dr. Brösamle



Kurilla

SCHERING AG - Corporate Patents

A la Oficina Europea de Patentes

Solicitud Internacional No. PCT/EP01/12005

Solicitante: Schering Aktiengesellschaft

Nuestra referencia: 51869AWOM1XX00+P

Respuesta a la Opinión Escrita de acuerdo con la Regla 66

El solicitante quisiera aportar los siguientes comentarios en respuesta a la Opinión Escrita del 29 de abril de 2002:

Base de la Opinión (Ítem III)

El lenguaje estándar relativo a no-establecer opinión con respecto a cierto objeto aparece en el Ítem III de la Opinión Escrita. A este respecto, el solicitante hace notar que el Informe de Búsqueda Internacional enviado por correo el 21 de marzo de 2002 no indica que algún objeto no hubiera sido sometido a búsqueda. Tan es así que el informe está basado en los objetos de las reivindicaciones 1 á 9, desde que el documento "P" fue citado como relevante para estas reivindicaciones. En consecuencia, la pregunta de si la invención reivindicada presenta novedad, altura inventiva o es industrialmente aplicable debería ser referido en el Informe de Examen Preliminar Internacional a todos los objetos reivindicados, específicamente a las reivindicaciones 1 - 9.

Declaración razonada con respecto a novedad, altura inventiva y aplicación industrial (Ítem V)

La Opinión Escrita indica que la invención, al menos como está definida en alguna de las reivindicaciones, no presenta novedad o

inventiva a la vista del Informe de Búsqueda Internacional y a los objetos a los que se dirigió la búsqueda.

El Informe de Búsqueda Internacional citó un documento con "X", el DE 197 06 061 A. Este documento, sin embargo, es solo relevante para las reivindicaciones 1,3 - 6, 8 y 9, de modo que, por lo menos el objeto de las reivindicaciones 2 y 7 debería ser confirmado como nuevo e inventivo. En cuanto al objeto de las reivindicaciones 1,3 - 6,8 y 9, el documento citado revela meramente que los compuestos de una fórmula general pueden ser adecuados a varias indicaciones. La indicación predominante es la contracepción y el control de la fertilidad post-coital (véase página 4, líneas 47-51). Otras indicaciones mencionadas son el tratamiento de anormalidades hormonales, incluyendo la menstruación o período post parto, la terapia de reemplazo hormonal y el tratamiento de la dismenorrea, endometriosis y cáncer hormona-dependiente (página 4, líneas 52 - 57). Sin embargo, no se indica que el compuesto específico 11beta-(4-acetilfenil)-17beta-hidroxi-17alfa-(1,1,2,2,2-pentafluoroetil)-estra-4,9-dien-3-ona pueda ser usado para el tratamiento o la profilaxis de una enfermedad hormona-dependiente. El solicitante revela por la primera vez el uso específico de este compuesto particular, y más aún, brinda fuerte evidencia de que el 11beta-(4-acetilfenil)-17beta-hidroxi-17alfa-(1,1,2,2,2-pentafluoroetil)estra-4,9-dien-3-ona pueda ser usado tanto para el tratamiento como para la profilaxis de una enfermedad hormona-dependiente en modelos de animal estándar, como p. ej. cáncer de mama. En consecuencia, el

objeto de la reivindicación 1, así como los objetos de sus reivindicaciones subordinadas 2 a 9, debe ser considerado nuevo e inventivo más allá del documento citado como "X".

Finalmente, el documento "P" citado en el Informe de Búsqueda Internacional no tiene relevancia para la presente solicitud. Como el texto de la solicitud internacional es básicamente idéntico con el texto de los certificados de prioridad, el objeto de la invención tiene derecho a la prioridad de fecha 18 de octubre de 2000. Por lo tanto, el documento publicado en diciembre de 2000 no es arte previo.

Considerando los argumentos precedentes, el solicitante solicita por el presente el informe de Examen Preliminar Internacional.

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

SCHERING AKTIENGESELLSCHAFT
Müllerstr. 178
13353 Berlin
ALLEMAGNE

AFB

ON

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PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing
(day/month/year)

23.01.2003

Applicant's or agent's file reference
51869AWOM1XX

IMPORTANT NOTIFICATION

International application No.
PCT/EP01/12005 ✓

International filing date (day/month/year)
17/10/2001 ✓

Priority date (day/month/year) =
18/10/2000

Applicant

SCHERING AKTIENGESELLSCHAFT et al.

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

4. REMINDER

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

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

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

For the purpose of deciding whether the claimed invention is patentable or not, the elected Offices may apply criteria additional to or different from the criteria on which the international preliminary examination report is based (see Articles 27(5), 33(5)). Additional criteria may include e.g. exemptions from patentability and the requirements of enabling disclosure and of clarity and support of claims.

Name and mailing address of the IPEA/



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Tratado de Cooperación en Materia de Patentes

De la Autoridad de Examen Preliminar Internacional

A Schering Aktiengesellschaft

Notificación de comunicación del informe de Examen Preliminar Internacional (Regla PCT 71.1)

Fecha de envío postal: 23/01/2003

Referencia del solicitante o agente: 51869AWOM1XX

Notificación Importante

Solicitud Internacional No. PCT/EP01/12005

Fecha de presentación internacional: 17/10/2001

Fecha de Prioridad: 18/10/2000

Solicitante: Schering Aktiengesellschaft y otros

1. El solicitante es notificado por la presente que esta Autoridad de Examen Preliminar Internacional transmite el Informe de Examen Preliminar Internacional y sus anexos, en caso de haberlos, realizado en la solicitud internacional.
2. Una copia del informe y sus anexos, en caso de haberlos, está siendo transmitido a la Oficina Internacional para que sea comunicado a todas las oficinas elegidas.
3. La Oficina Internacional preparará una traducción al inglés del informe (pero no de todos los anexos) y transmitirá dicha traducción a las oficinas elegidas que la requieran.
4. Recordatorio: El solicitante debe iniciar la fase nacional en cada oficina elegida mediante la realización de ciertos actos (presentación de traducciones y pago de impuestos nacionales)

dentro de los 30 meses contados desde la fecha de prioridad (o más tarde en algunas oficinas) Artículo 39(1)) (Véase también el recordatorio enviado por la Oficina Internacional con el Formulario PCT/IB/301).

Donde la traducción de la solicitud internacional debe ser entregada a una oficina elegida, esa traducción debe contener una traducción de cada anexo al informe de examen preliminar internacional. Es responsabilidad del solicitante el preparar y proveer dicha traducción directamente a cada una de las oficinas elegidas.

Para más detalles a los límites de tiempo aplicables y requerimientos de las oficinas elegidas, véase el Volumen II de la Guía del solicitante de PCT.

A fin de decidir si la invención reivindicada es patentable o no, las oficinas elegidas pueden aplicar criterios adicionales o diferentes de los criterios sobre los que está basado el informe de examen preliminar internacional (véase Artículos 27(5), 33(5)). Los criterios adicionales pueden incluir p. ej. excepciones a la patentabilidad y el requerimiento de permiso la divulgación y de claridad y soporte de las reivindicaciones.



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Bescheinigung

Certificate

Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. Patent application No. Demande de brevet n°

00250341.5

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

I.L.C. HATTEN-HECKMAN

DEN HAAG, DEN
THE HAGUE,
LA HAYE, LE

28/02/01



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**Blatt 2 der Bescheinigung
Sheet 2 of the certificate
Page 2 de l'attestation**

Anmeldung Nr.:
Application no.: 00250341.5
Demande n°:

Anmeldetag:
Date of filing: 18/10/00
Date de dépôt:

Anmelder:
Applicant(s):
Demandeur(s):
Schering Aktiengesellschaft
13353 Berlin
GERMANY

Bezeichnung der Erfindung:
Title of the invention:
Titre de l'invention:

Use of antiprogestins for prophylaxis and treatment of hormone-dependent diseases

In Anspruch genommene Priorität(en) / Priority(ies) claimed / Priorité(s) revendiquée(s)

Staat:
State:
Pays:

Tag:
Date:
Date:

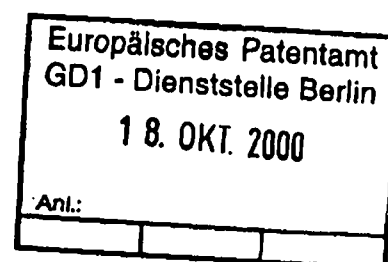
Aktenzeichen:
File no.
Numéro de dépôt:

Internationale Patentklassifikation:
International Patent classification:
Classification internationale des brevets:

/

Am Anmeldetag benannte Vertragsstaaten:
Contracting states designated at date of filing: AT/BE/CH/CY/DE/DK/ES/FI/FR/GB/GR/IE/IT/LI/LU/MC/NL/PT/SE/TR
Etats contractants désignés lors du dépôt:

Bemerkungen:
Remarks:
Remarques:



5 **USE OF ANTIPROGESTINS FOR PROPHYLAXIS AND
TREATMENT OF HORMONE-DEPENDENT DISEASES**

10 Field of the Invention

The present invention relates to the use of antiprogestins for the prophylaxis and treatment of hormone-dependent diseases, in particular breast cancer. The present invention further relates to pharmaceutical compositions and dosage forms comprising antiprogestins for the prophylaxis and treatment of hormone-dependent diseases, in particular breast cancer.

15 A particularly preferred antiprogestin for use in the invention is the antiprogestin 11 β -(4-acetylphenyl)-17 β -hydroxy-17 α -(1,1,2,2,2-pentafluoroethyl)-estra-4,9-dien-3-one or a pharmaceutically acceptable derivative or analogue thereof.

20 Background of the Invention

Endocrine therapy represents a mainstay of effective, minimally toxic, palliative treatment for metastatic breast cancer. As a standard palliative treatment of non-operable mammary carcinomas as well as for adjuvant therapy after primary treatment of mammary carcinomas predominantly the antiestrogen tamoxifen is used. However, tamoxifen cannot
25 cure breast cancer. Thus, for secondary therapy progestins or aromatase inhibitors are commonly used. In premenopausal women ovariectomy, tamoxifen and LHRH (luteinizing hormone releasing hormone) analogs achieve comparable results (H.T. Mouridson et al., *Eur. J. Cancer Clin. Oncol.*, 24, pp. 99-105, 1988).

30 Although tamoxifen is widely used for adjuvant therapy of breast cancer, its use as a chemopreventive agent is problematic, because it has been shown that the treatment

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results in an increase in the incidence of endometrial cancers (I.N. White, *Carcinogenesis*, 20(7):1153-60, 1999).

Antiprogestins represent a relatively new and promising class of therapeutic agents that could have significant impact on breast cancer treatment. Although antiprogestins were originally created with regard to medicinal non-surgical termination of pregnancy (EP 129 499), certain antiprogestins have recently gained importance in the endocrine therapy of those breast cancers involving receptors for progesterone (T. Maudelonde et al., in: J.G.M. Klijn et al., *Hormonal Manipulation of Cancer: Peptides, Growth Factors and New (Anti)*
10 *Steroidal Agents*, Raven Press, New York, 1987, pp. 55-59). This new strategy in endocrine therapy is based on the antitumor activity of antiprogestins in progesterone receptor-positive human breast cancer cell lines *in vitro* and in several hormone-dependent mammary tumors of the mouse and rat *in vivo*. In particular, the antitumor mechanism of the antiprogestins onapristone and mifepristone (RU 486) was investigated using the
15 hormone-dependent MXT mammary tumor model of the mouse as well as the DMBA- and the NMU-induced mammary tumor models of the rat (M. R. Schneider et al., *Eur. J. Cancer Clin. Oncol.*, Vol. 25, No. 4, pp. 691-701, 1989; H. Michna et al., *Breast Cancer Research and Treatment* 14:275-288, 1989; H. Michna, *J. Steroid. Biochem.* Vol. 34, Nos 1-6, pp. 447-453, 1989). However, due to low activity and adverse side effects involved
20 with e.g. mifepristone this compound could not be recommended as a single agent in the management of breast cancer (D. Perrault et al., *J. Clin. Oncol.* 1996 Oct, 14(10), pp.2709-2712).

Antiprogesterin compounds are suitable for initiating abortions and thus for use in postcoital
25 fertility control, as contraceptives for women (WO-A 93/23020, WO-A 93/21927) and further for the treatment of hormone irregularities, for initiating menstruation and for initiating labor. Further indications are in the field of hormone substitution therapy (WO-A 94/18983), the treatment of afflictions related to dysmenorrhea and the treatment of endometriosis (EP-A 0 266 303) as well as myomas.
30 17 α -fluoroalkylsteroids having strong antiprogesterin activity as well as methods for producing them are described in WO 98/34947.

Antiprogestins of the prior art tested or used previously due to their antitumor activity frequently exhibited certain disadvantages.

5 For example, despite the fact that prior art antiprogestins exhibited antigestagenic activity, these compounds were not suitable treatments for hormone-dependent diseases such as breast cancer. In particular, prior art compounds were associated with side effects, e.g. mifepristone exhibits strong antiglucocorticoid side effects (cf. L.M. Kettel et al., *Fertil. Steril.* 1991 Sep, 56(3), pp. 402-407; X. Bertagna, *Psychoneuroendocrinology* 1997; 22
10 Suppl. 1, pp. 51-55) and besides it showed only moderate activity in clinical trials (see again D. Perrault et al., *J. Clin. Oncol.* 1996 Oct, 14(10), pp.2709-2712). Regarding side effects of other hormone-based therapies, as already mentioned above, tamoxifen administration can result in an increase in the incidence of endometrial cancers (I.N. White, *Carcinogenesis*, 20(7):1153-60, 1999).

15

Another problem with prior art antiprogestins was poor bioavailability when administered orally. Thus, they generally had to be administered in high doses, giving rise to possible unfavorable side effects. Moreover, oral administration is desirable with respect to patient convenience and compliance.

20

Furthermore, there is still a need for compounds that are active not only in the treatment, but also in the prophylaxis of breast cancer and other hormone-dependent diseases. The increased incidence of endometrial cancer associated with tamoxifen tends to show that this compound is unsuitable for prophylaxis treatment of healthy women, and no other
25 suitable compounds are available (cf. L. Bergman et al., *The Lancet*, Vol. 356, Sept. 9, 2000; 881-887).

30 Object of the Present Invention

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It is an object of the present invention to prevent or reduce the disadvantages of the prior art methods for preventing or treating hormone-dependent diseases, such as breast cancer. It is especially desired that a means of preventing and treating hormone-dependent diseases, such as breast cancer, via the administration of highly effective agents is provided that is superior to known methods and agents, including ovariectomy. Thus it is further especially desired to provide a treatment of hormone-dependent diseases, such as breast cancer, that prevents serious and risk-laden surgery involved with ovariectomy. It is further desired to provide an agent for use according to the invention exhibiting less side effects than previously known or suggested methods for treating and preventing hormone-dependent diseases such as breast cancer.

It is a further object of the present invention to provide pharmaceutical compositions comprising highly effective antitumor agents for the prophylaxis and treatment of breast cancer and other hormone-dependent diseases.

These objects are surprisingly achieved by the use of antiprogestins according to the present invention and by pharmaceutical compositions and dosage forms comprising such antiprogestins. Particularly preferred in this regard is the antiprogestin 11β -(4-acetylphenyl)- 17β -hydroxy- 17α -(1,1,2,2,2-pentafluoroethyl)-estra-4,9-dien-3-one or a pharmaceutically acceptable derivative or analogue thereof.

It is a further object of the present invention to provide antiprogestins, such as the antiprogestin 11β -(4-acetylphenyl)- 17β -hydroxy- 17α -(1,1,2,2,2-pentafluoroethyl)-estra-4,9-dien-3-one or pharmaceutically acceptable derivatives or analogues thereof, that are particularly suitable for oral administration.

Summary of the Invention

The present invention is based on the novel and unexpected observation that certain antiprogestins, in particular 11β -(4-acetylphenyl)- 17β -hydroxy- 17α -(1,1,2,2,2-pentafluoroethyl)-estra-4,9-dien-3-one or a pharmaceutically acceptable derivative or analogue thereof, are exceptionally active in the prevention and reduction of tumor growth

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in DMBA (7,12-dimethylbenzanthracene)- and NMU (N-methylnitrosourea)-induced breast cancer models. In fact, the antiprogesterin 11 β -(4-acetylphenyl)-17 β -hydroxy-17 α -(1,1,2,2,2-pentafluoroethyl)-estra-4,9-dien-3-one (I) turned out to be distinctly more potent than tamoxifen and ovariectomy in the prevention of breast cancer development.

5

Thus, the present invention provides a method for prophylaxis and treatment of breast cancer and other hormone-dependent diseases in mammals, in particular humans, in need of such treatment, said method comprising administering a pharmaceutically effective amount of an antiprogesterin, in particular 11 β -(4-acetylphenyl)-17 β -hydroxy-17 α -(1,1,2,2,2-pentafluoroethyl)-estra-4,9-dien-3-one, or a pharmaceutically acceptable derivative thereof or analogue thereof, to a patient.

10

The present invention further provides pharmaceutical compositions comprising an antiprogesterin, in particular 11 β -(4-acetylphenyl)-17 β -hydroxy-17 α -(1,1,2,2,2-pentafluoroethyl)-estra-4,9-dien-3-one or a pharmaceutically acceptable derivative or analogue thereof, in an amount sufficient for the prophylaxis or treatment of breast cancer or other hormone-dependent diseases.

15

The preferred antiprogesterin 11 β -(4-acetylphenyl)-17 β -hydroxy-17 α -(1,1,2,2,2-pentafluoroethyl)-estra-4,9-dien-3-one will hereinafter be referred to as "antiprogesterin (I)".

20

Brief Description of the Figures

Figure 1 shows the tumor development prevention effect of antiprogesterin (I) in the DMBA-induced mammary carcinoma of the rat, compared with a control, tamoxifen and ovariectomy.

25

Figure 2 shows the tumor growth inhibiting effects of antiprogesterin (I) in a dose-response study in the DMBA-induced mammary carcinoma of the rat, compared with a control, the antiprogesterin onapristone as well as ovariectomy. The study was performed with 0.5, 2.0, 5.0 and 10.0 mg/kg s.c. doses of antiprogesterin (I).

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Figure 3 shows the tumor development prevention effect of antiprogesterin (I) in the NMU-induced mammary carcinoma of the rat, compared with a control, the antiestrogens raloxifen and tamoxifen, the aromatase inhibitor letrozol as well as ovariectomy.

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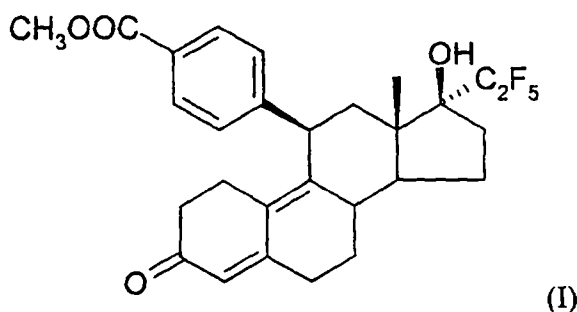
Figure 4 shows the tumor growth inhibiting effect of 0.5 and 1.0 mg/kg doses of antiprogesterin (I) in the NMU-induced mammary carcinoma of the rat, compared with a control, onapristone (5 mg/kg) and ovariectomy.

10 Figure 5 shows the tumor growth inhibiting effect of antiprogesterin (I) in a 10 mg/kg s.c. dose in the T47D human xenograft in scid mice, compared to a control as well as ovariectomy.

Figure 6 shows the tumor growth inhibiting effect of antiprogesterin (I) in a 10 mg/kg s.c. dose in the MCF7 human xenograft in scid mice, compared to a control as well as ovariectomy.

Detailed Description of the Invention

20 Antiprogesterin (I) — 11 β -(4-acetylphenyl)-17 β -hydroxy-17 α -(1,1,2,2,2-pentafluoroethyl)-estra-4,9-dien-3-one — is represented below by formula (I):



25 Antiprogesterin (I) (or a pharmaceutically acceptable derivative or analogue thereof having comparable activity) is a valuable pharmaceutical agent having strong antiprogesterin activity. Antiprogesterin (I), as well as further antiprogesterins, can be used according to the

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present invention for the prophylaxis and treatment of breast cancer and other hormone-dependent diseases.

The term "antiprogesterin" in the context of the present invention is intended to primarily
5 comprise all compounds being capable of competitively inhibiting progesterone receptors. However, it should also encompass compounds capable of inhibiting the biosynthesis of progestins.

A pharmaceutically acceptable derivative or analogue of antiprogesterin (I) in the context of
10 the present invention may include, for example, any one of the inventive compounds disclosed in WO 98/34947.

The term "hormone-dependent diseases" in the context of the present invention may include, but is not limited to, breast cancer, ovarian cancer, endometrial cancer, myeloma,
15 anovulatory infertility, meningoma, i.e. diseases which substantially originate or are influenced by the presence of hormone receptors and/or hormone-dependent pathways.

As regards the superiority of the present invention over the prior art, it is especially favorable that, e.g., in antiprogesterin (I) used according to the present invention further
20 endocrine side effects, such as e.g. androgen, estrogen or antiglucocorticoid activity are only very weak, if present at all. Due to the high bioavailability of antiprogesterin (I) it can be administered orally, thus rendering the treatment for a patient in need thereof as convenient as possible. As a further favorable consequence, antiprogesterin (I) is well tolerated and can be administered in relatively low doses compared to established
25 treatments thus reducing undesirable side effects, such as an increase in the incidence of endometrial cancers with the administration of tamoxifen (see I.N. White, *Carcinogenesis*, 20(7):1153-60, 1999; L. Bergman et al., *The Lancet*, Vol. 356, Sept. 9, 2000, 881-887) as well as the antiglucocorticoid effects and certain toxic side effects related to the administration of mifepristone (see D. Perrault et al., *J. Clin. Oncol.* 1996 Oct, 14(10),
30 pp.2709-2712; L.M. Kettel et al., *Fertil. Steril.* 1991 Sep, 56(3), pp.402-407; X. Bertagna, *Psychoneuroendocrinology* 1997, 22 Suppl. 1; pp. 51-55).

A further advantage of the present invention over the prior art is the provision of an effective method for the prophylaxis of hormone-dependent diseases such as breast cancer, such that patients under high risk of developing or re-developing hormone-dependent diseases can be treated in advance to avoid incidence of such diseases.

In a first aspect the present invention relates to a method for the prophylaxis or treatment of breast cancer and other hormone-dependent diseases, comprising administering at least one antiprogesterin, preferably antiprogesterin (I) or a pharmaceutically acceptable derivative or analogue thereof to a mammal, preferably a human, in need of such prophylaxis or treatment.

In a further aspect the present invention relates to the use of antiprogesterins as defined above, preferably antiprogesterin (I) or a pharmaceutically acceptable derivative or analogue thereof, for the manufacture of a medicament, in particular for the prophylaxis or treatment of breast cancer or other hormone-dependent diseases.

In another aspect the present invention relates to pharmaceutical compositions comprising at least one antiprogesterin as defined above, preferably antiprogesterin (I) or a pharmaceutically acceptable derivative or analogue thereof. Optionally the antiprogesterin (I) can be combined with other pharmacologically active agents. For example, the antiprogesterin may also be combined with a cytotoxic agent for treatment by coupling to a hormone receptor.

The manufacture of the medicaments may be performed according to methods known in the art. Commonly known and used adjuvants as well as further suitable carriers or diluents may be used. Suitable carriers and adjuvants may be such as recommended for pharmacy, cosmetics and related fields in: *Ullmann's Encyclopedia of Technical Chemistry*, Vol. 4, (1953), pp. 1-39; *Journal of Pharmaceutical Sciences*, Vol. 52 (1963), p. 918ff; H.v.Czetsch-Lindenwald, "Hilfsstoffe für Pharmazie und angrenzende Gebiete";

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Pharm. Ind. 2, 1961, p.72ff; Dr. H.P. Fiedler. *Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete*. Cantor KG, Aulendorf in Württemberg, 1971.

Antiprogestins suitable for the purposes of the present invention, preferably antiprogestin
5 (I) or a pharmaceutically acceptable derivative or analogue thereof, can be incorporated
into pharmaceutical compositions according to known methods of preparing galenics for
oral or parenteral, e.g., intraperitoneal, intramuscular, subcutaneous or percutaneous
application. They can also be implanted into tissue. Implants can comprise as inert
materials e.g. biologically degradable polymers or synthetic silicones such as e.g. silicone
10 rubber.

They can be administered in the form of tablets, pills, dragees, gel capsules, granules,
suppositories, implants, injectable sterile aqueous or oily solutions, suspensions or
emulsions, ointments, creams, gels or by intravaginal (e.g., vaginal rings) or intrauterine
15 systems (e.g., diaphragms, loops).

For the preparation of pharmaceutical compositions for oral administration, the
antiprogestins suitable for the purposes of the present invention as defined above can be
admixed with commonly known and used adjuvants and carriers such as for example, gum
20 arabic, talcum, starch, sugars such as, e.g., mannitose, methyl cellulose, lactose, gelatin,
surface-active agents, magnesium stearate, aqueous or non-aqueous excipients, paraffin
derivatives, cross-linking agents, dispersants, emulsifiers, lubricants, conserving agents
and flavoring agents (e.g., ethereal oils). In the pharmaceutical composition, the
antiprogestin may be dispersed in a microparticle, e.g. a nanoparticulate, composition.

25 In order to further enhance the bioavailability of the active agent, the antiprogestins
suitable for the purposes of the present invention as defined above can also be formulated
as cyclodextrin clathrates by reacting them with α -, β - or γ -cyclodextrines or derivatives
thereof according to the method as disclosed in PCT/EP95/02656.

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For parenteral administration the antiprogestins suitable for the purposes of the present invention as defined above can be dissolved or suspended in a physiologically acceptable diluent, such as, e.g., oils with or without solubilizers, surface-active agents, dispersants or emulsifiers. As oils for example and without limitation, olive oil, peanut oil, cottonseed
5 oil, soybean oil, castor oil and sesame oil may be used.

The amount to be administered (i.e., a "pharmaceutically effective amount") varies within a broad range and depends on the condition to be treated and the mode of administration. It can cover any amount efficient for the intended treatment. Determining a
10 "pharmaceutically effective amount" is within the purview of the person skilled in the art.

One unit dose may represent about 0.1 to 100 mg active agent(s). For administration to humans, the daily dose of the active agent(s) is about 0.1 to 400 mg, preferably 10 to 100 mg, most preferably 50 mg.

15

The pharmaceutical compositions according to the present invention can also be administered via a depot injection, an implant preparation or an IUD (internal uterine device), optionally for sustained delivery of the active agent(s).

20 The preferred mode of administration is oral administration. The antiprogestins for use according to the invention, and in particular, antiprogestin (I) or a pharmaceutically acceptable derivative or analogue thereof are particularly suitable for oral administration.

According to all aspects of the present invention it is also possible to combine at least one
25 antiprogestin as defined above, in particular antiprogestin (I) or a pharmaceutically acceptable derivative or analogue thereof, with at least one antiestrogen, because many hormone-dependent diseases, in particular breast cancer, exhibit not only progesterone receptors, but also estrogen receptors. The antiestrogen may be administered either simultaneously with or sequentially to the antiprogestin, and in particular with/to
30 antiprogestin (I) or a pharmaceutically acceptable derivative or analogue thereof. The amount of antiprogestin and antiestrogen may be equal or one component may be more

predominant than the other, such as in an antiprogestin:antiestrogen ratio of 1:50 to 50:1, preferably 1:30 to 30:1, and most preferably 1:15 to 15:1.

Examples of suitable antiestrogens for use according to the invention are non-steroidal antiestrogens, such as tamoxifen and nafoxidine as well as raloxifen and EM800 and the steroidal antiestrogen faslodex. Examples of steroidal antiestrogens include those disclosed in EP 0 348 341 A and those disclosed in WO 98/07740, in particular, 11 β -flouro-7 α -{5-[N-methyl-N-3-(4,4,5,5,5-pentafluoropentylthio-propylamino)-pentyl]}-estra-1,3,5(10)-trien-3,17 β -diol, or those disclosed in WO 99/33855, in particular 11 β -flouro-7 α -{5-[methyl-(7,7,8,8,9,9,10,10,10-nonafluoro-decyl)-amino]-pentyl}-estra-1,3,5(10)-trien-3,17 β -diol or pharmaceutically acceptable derivatives or analogues thereof. Aromatase inhibitors having an antiestrogenic effect, such as those disclosed on pages 7 to 8 of EP 0 495 825 B1 may also be used as antiestrogens.

- 15 The invention is further illustrated in the examples. The following examples are not to be understood as a limitation.

Examples

20 Example 1:

DMBA-induced breast cancer model in rat (prevention experiment)

Materials and Methods:

- 25 Immature female Sprague-Dawley rats (49 - 51 days old; 10 animals/group) were used in this study. The carcinogen 7,12-dimethylbenz[a]anthracene (DMBA) was given as a single oral administration (10 mg). Treatment was started 20 days later as followed: 1) solvent control, 2) ovariectomy at treatment start, 3) tamoxifen, 1 mg/kg s.c., 4) antiprogestin (I), 3 mg/kg, s.c., 6 days/week. Rats were examined weekly for breast
30 tumors by paipation. As a parameter for the prophylactic effect the tumor incidence (number of animals/group with tumors in %) was determined. For a further description

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and evaluation of DMBA and NMU prevention models, see R.G. Metha, *European Journal of Cancer* 36 (2000), pp. 1275-1282.

Results:

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In the control group all rats developed mammary tumors within 10 weeks after treatment start (incidence 100%) and progressive tumor growth was observed. Prophylactic treatment with the antiprogesterin (I) prevented the tumor development for 12 weeks completely, and at the end of the experiment, after 22 weeks, in only one rat a tumor was
10 detected (incidence 10%). After ovariectomy at the end of the experiment 40% of the rats had developed tumors. In comparison, treatment with the antiestrogen tamoxifen reduced the tumor incidence only to 60% (see fig. 1)

Conclusion:

15

In the DMBA-induced mammary tumor model in the rat, the antiprogesterin (I) completely suppressed the tumor development in intact animals for more than 12 weeks after treatment start. Figure 1 clearly shows the superiority in activity of antiprogesterin (I) over the conventional anti-breast cancer reagent tamoxifen and even over standard estrogen
20 deprivation therapy (ovariectomy) with respect to prophylactic treatment. Antiprogesterin (I) is thus superior to the established standard therapy for preventing breast cancer in women under high risk of developing the disease (tamoxifen prophylactic therapy).

These and the following results indicate that the use of antiprogesterin (I) for the
25 prophylaxis and treatment of breast cancer is superior to established standard treatments.

30

Example 2:DMBA-induced breast cancer model in rat (therapy experiment/dose-response study)

Materials and Methods:

5

Immature female Sprague-Dawley rats (49 - 51 days old; 10 animals/group) were used in this study. Mammary tumors were induced by a single oral administration of 10 mg 7,12-dimethylbenz[a]anthracene (DMBA, Serva/Heidelberg). Rats with at least one established tumor with a size of more than 150 mm² were treated for 4 weeks by: 1) solvent control, 2) ovariectomy at treatment start, 3) antiprogesterin (I), 0,5 mg/kg s.c., 4) antiprogesterin (I), 2 mg/kg s.c., 5) antiprogesterin (I), 5 mg/kg s.c., 6) antiprogesterin (I), 10 mg/kg s.c., and 7) onapristone, 5 mg/kg, s.c., daily. As a parameter for growth inhibition the change of tumor area (in % with respect to initial tumor size) determined by weekly caliper measurements was used. For statistical analysis of intergroup differences of mean values the Kruskal-

15 Wallis-test was used.

Results:

In intact control animals, progressive tumor growth was observed, whereas ovariectomy caused a considerable tumor regression in 90% of the animals. Treatment with antiprogesterin (I) at doses of or above 2 mg/kg resulted in a significant inhibition of tumor growth compared with the control (see fig. 2). There was a clear dose-response relationship. Whereas treatment with 0.5 mg/kg antiprogesterin (I) did not significantly prevent the tumor from growing, at 2 mg/kg maximal growth inhibition was observed. In this group a complete tumor regression was seen in 50% of the rats. The effect of the highest dose of antiprogesterin (I) tested in this experiment (10 mg/kg), was comparable to that of 2 mg/kg. Onapristone (5 mg/kg, s.c.) was distinctly less effective than antiprogesterin (I) at comparable doses.

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Conclusion:

In the DMBA-induced mammary tumor model in the rat, antiprogesterin (I) completely suppresses the tumor growth in intact animals. It was found that 2 mg/kg antiprogesterin (I) has a maximal effect on tumor growth. Antiprogesterin (I) was distinctly superior to onapristone.

Example 3:

10 NMU-induced breast cancer model in rat (prevention experiment)

Materials and Methods:

Tumors were induced by a single intravenous injection of NMU (nitrosomethylurea, 50 mg/kg) in female Sprague-Dawley rats (obtained from Tierzucht Schönwalde, age 50-55 days). Treatment was started 10 days later as followed: 1) solvent control, 2) ovariectomy at treatment start, 3) tamoxifen, 3 mg/kg s.c., 4) antiprogesterin (I), 3 mg/kg, s.c., 5) letrozole, 3 mg/kg s.c., 6) raloxifen, 3 mg/kg s.c., 6 days/week. Rats were examined weekly for breast tumors by palpation. As a parameter for the prophylactic effect the tumor incidence (number of animals/group with tumors in %) was determined. For a further description and evaluation of DMBA and NMU prevention models, see R.G. Metha, *European Journal of Cancer* 36 (2000), pp. 1275-1282.

Results:

25

In the control group all rats developed mammary tumors within 10 weeks after treatment start (incidence 100%; see fig. 3) and progressive tumor growth was observed. Prophylactic treatment with the antiprogesterin (I) prevented the tumor development for 12 weeks completely, and at the end of the experiment, after 27 weeks, in only one rat a tumor was detected (incidence 10%). In comparison, in treatment with the other antiestrogens or the aromatase inhibitor letrozole the tumor incidence was reduced only to

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20 - 60%. After ovariectomy at the end of the experiment 20% of the rats had developed tumors.

Conclusion:

5

In the NMU-induced mammary tumor model in the rat, antiprogesterone (I) completely suppressed the tumor development in intact animals for more than 12 weeks after treatment start. The effect of the prophylactic treatment by antiprogesterone (I) was superior to that of conventional antiestrogens for breast cancer therapy (i.e., raloxifen, tamoxifen) and aromatase inhibitor letrozol and to standard estrogen deprivation therapy (ovariectomy) regarding tumor incidence and tumor growth.

10

As in the DMBA-induced tumor model (see Example 1), these results indicate that antiprogesterone (I) effectively prevents the development of breast tumors in a manner which is superior to the standard prophylactic treatment, e.g. with tamoxifen.

15

Example 4:

NMU-induced breast cancer model in rat (therapy experiment)

20

Materials and Methods:

25

Tumors were induced by a single intravenous injection of NMU (nitrosomethylurea, 50 mg/kg) in female Sprague-Dawley rats (obtained from Tierzucht Schönwalde, age 50-55 days). Starting 10 days later, rats with at least one established tumor were treated for 4 weeks by: 1) solvent control, 2) ovariectomy at treatment start, 3) antiprogesterone (I), 1.0 mg/kg/day, 4) antiprogesterone (I), 0.5 mg/kg/day and 5) onapristone, 5 mg/kg/day. As a parameter for growth inhibition the change of tumor area (in % of initial tumor size) determined by weekly caliper measurements was used. For statistical analysis of intergroup differences of mean values the Kruskal-Wallis-test was used.

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Results:

In intact control animals, progressive tumor growth was observed, whereas ovariectomy caused a complete tumor growth inhibition. Treatment with antiprogesterin (I) at doses of 0.5 or 1.0 mg/kg resulted in a significant inhibition of tumor growth compared with the control (see fig. 4). Onapristone (5 mg/kg) was distinctly less effective than antiprogesterin (I) at the much lower dose of 0.5 mg/kg.

Conclusions:

10

In the MNU-induced mammary tumor model in the rat, antiprogesterin (I) completely suppresses the tumor growth in intact animals. It was found that at a dose of 1.0 mg/kg and even at a dose of only 0.5 mg/kg antiprogesterin (I) has a significant effect on tumor growth. Thus, antiprogesterin (I) was superior to known antiprogesterins like onapristone.

15

Example 5:T47D Human xenograft (therapy experiment)

20 Materials and Methods:

Female Fox Chase scid mice (M&B) were supplemented with estradiol pellets (Innovative Research of America). T47D breast cancer cells, obtained from cell culture and suspended in matrigel, were implanted s.c. in the inguinal region of the mice. Treatment was started when the tumors were approximately 25 mm² in size. Treatment was continued until progression of the tumors. Experimental groups were: 1) control (vehicle), 2) ovariectomy, 3) antiprogesterin (I), 10 mg/kg s.c.. Tumor area was determined by caliper measurements. The Kruskal Wallis test was used for statistical analysis of intergroup differences of mean values.

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Results:

In the T47D breast cancer model, ovariectomy resulted in a considerable inhibition of tumor growth, compared with the rapid growth in the control. Fig. 5 shows that the s.c. application of 10 mg/kg antiprogesterin (I) also caused an inhibition of tumor growth, almost comparable to the effect of conventional estrogen deprivation therapy (ovariectomy).

Conclusion:

The effect of antiprogesterin (I) in inhibiting the growth of the human T47D breast cancer xenografted in Fox Chase scid mice is comparable to the effect of standard estrogen deprivation therapy (ovariectomy) which is considered to be the maximum effective method of inhibiting growth of breast cancer in this model.

Example 6:MCF7 Human xenograft (therapy experiment)

Materials and Methods:

Female Fox Chase scid mice (M&B) were supplemented with estradiol pellets (Innovative Research of America). MCF7 breast cancer cells, obtained from cell culture and suspended in matrigel, were implanted s.c. in the inguinal region of the mice. Treatment was started when the tumors were approximately 25 mm² in size. Treatment was continued until progression of the tumors. Experimental groups were: 1) control (vehicle), 2) ovariectomy, 3) antiprogesterin (I), 10 mg/kg s.c. Tumor area was determined by caliper measurements. The Kruskal Wallis test was used for statistical analysis of intergroup differences of mean values.

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Results:

In the MCF7 breast cancer model, ovariectomy resulted in a considerable inhibition of tumor growth, compared with the rapid growth in the control. Fig. 6 shows that the s.c. application of 10 mg/kg antiprogesterin (I) also caused an inhibition of tumor growth, almost comparable to the effect of conventional estrogen deprivation therapy (ovariectomy).

Conclusion:

The effect of antiprogesterin (I) in inhibiting the growth of the human MCF7 breast cancer xenografted in Fox Chase scid mice is comparable to the effect of standard estrogen deprivation therapy (ovariectomy) which is considered to be the maximum effective method of inhibiting growth of breast cancer in this model.

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Europäisches Patentamt
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1 8. OKT. 2000

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CLAIMS

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1. Use of the antiprogesterin 11β -(4-acetylphenyl)- 17β -hydroxy- 17α -(1,1,2,2,2-pentafluoroethyl)-estra-4,9-dien-3-one or a pharmaceutically acceptable derivative or analogue thereof for the manufacture of a medicament for the prophylaxis or treatment of a hormone-dependent disease in a mammal.

10

2. Use according to claim 1, wherein the disease is breast cancer.

3. Use according to claims 1 or 2, wherein the mammal is a human.

15

4. Use according to any preceding claim, wherein the medicament is administered orally.

20

5. Use according to any preceding claim, wherein the antiprogesterin 11β -(4-acetylphenyl)- 17β -hydroxy- 17α -(1,1,2,2,2-pentafluoroethyl)-estra-4,9-dien-3-one is administered in a unit dose of 50 mg.

25

6. Pharmaceutical composition comprising the antiprogesterin 11β -(4-acetylphenyl)- 17β -hydroxy- 17α -(1,1,2,2,2-pentafluoroethyl)-estra-4,9-dien-3-one or a pharmaceutically acceptable derivative or analogue thereof in an amount sufficient for the prophylaxis or treatment of a hormone-dependent disease in a mammal.

30

7. Pharmaceutical composition according to claim 6, wherein the disease is breast cancer.

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8. Pharmaceutical composition according to claims 6 or 7, wherein the mammal is a human.

5 9. Pharmaceutical composition according to any one of claims 6 to 8, further comprising an antiestrogen.

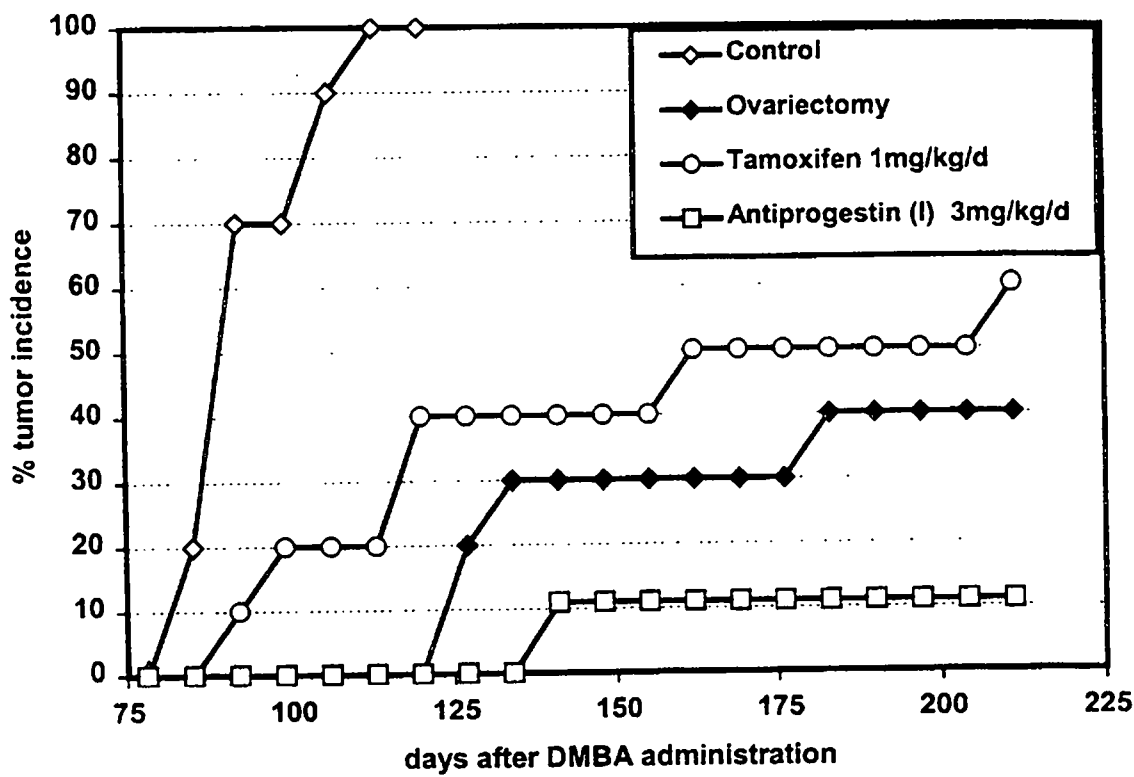
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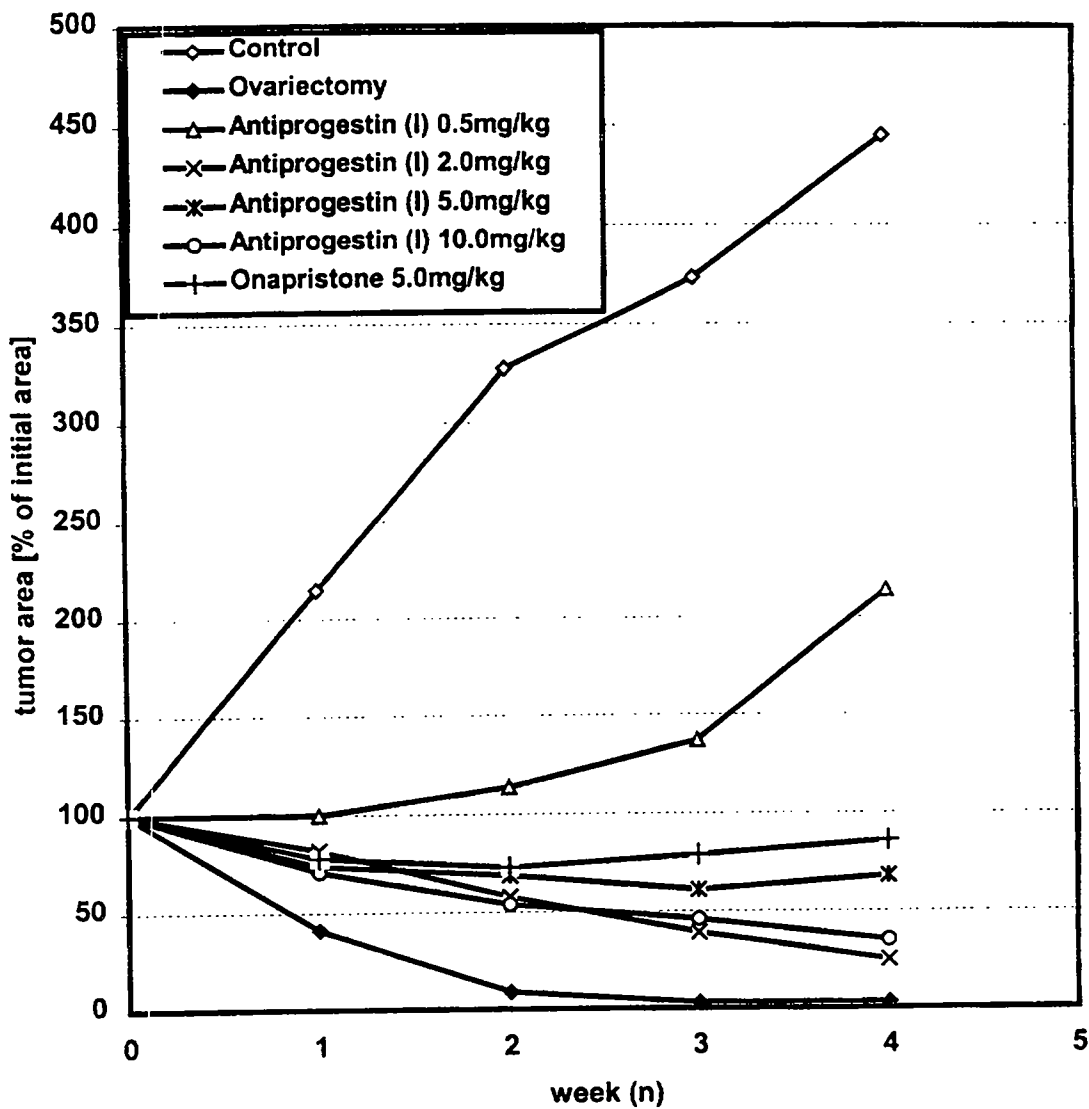
FIG. 1



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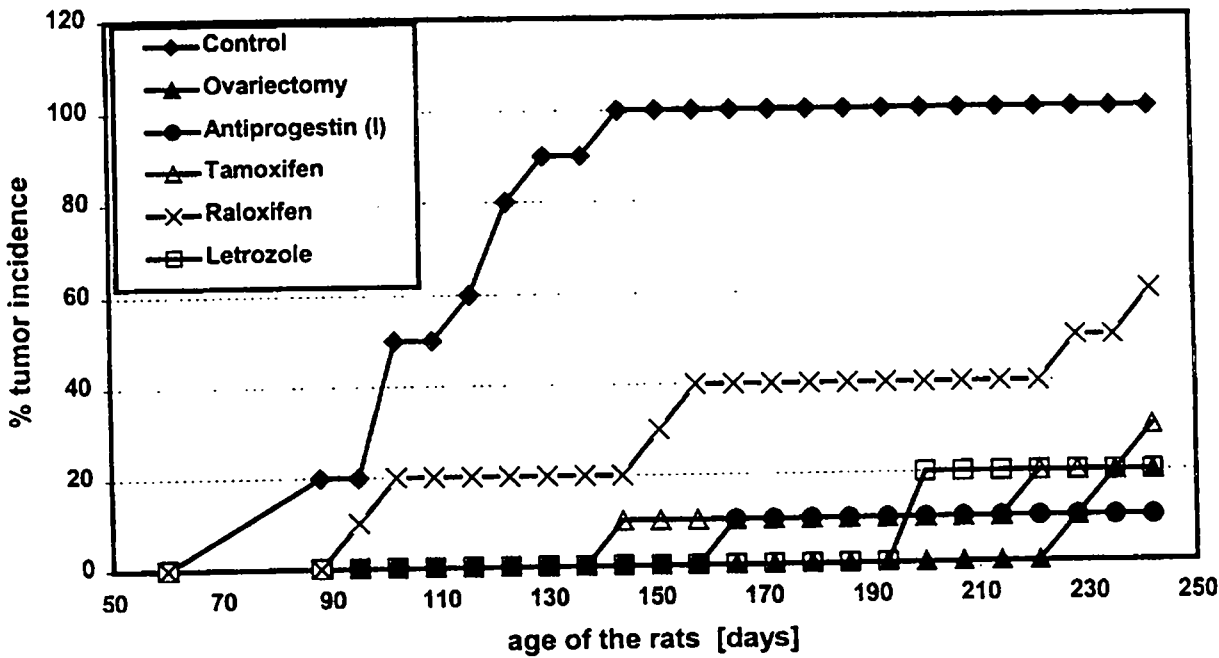
FIG. 2



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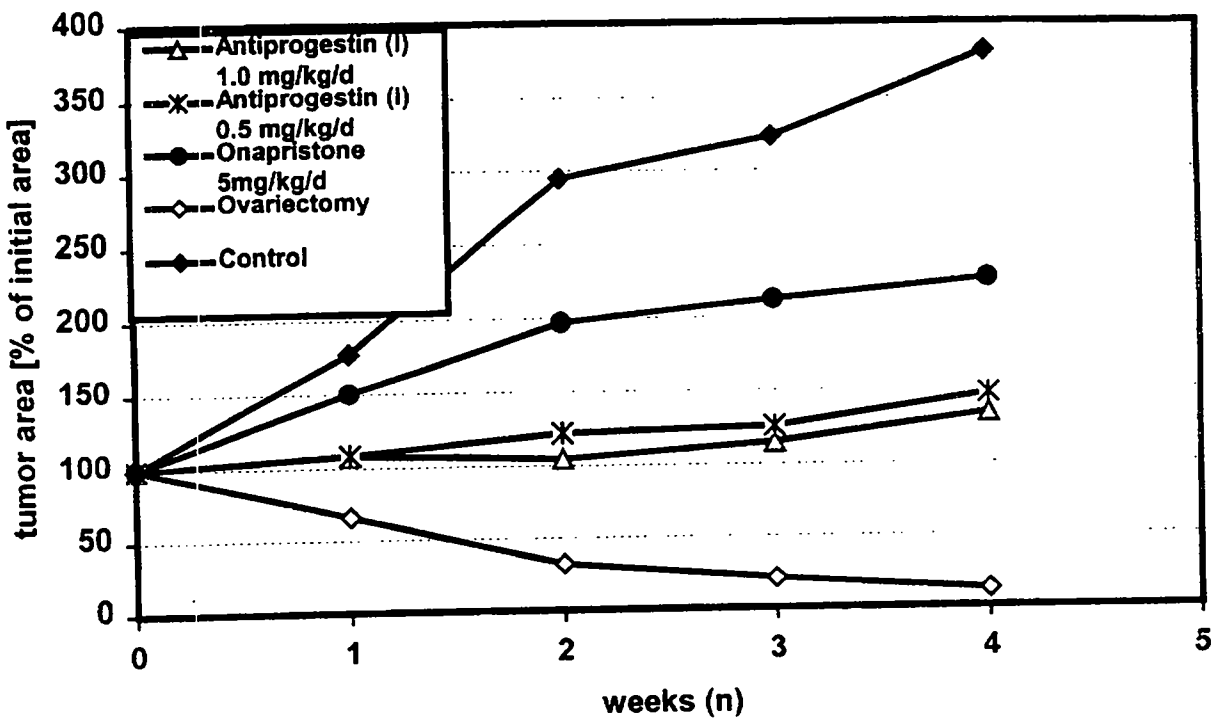
FIG. 3



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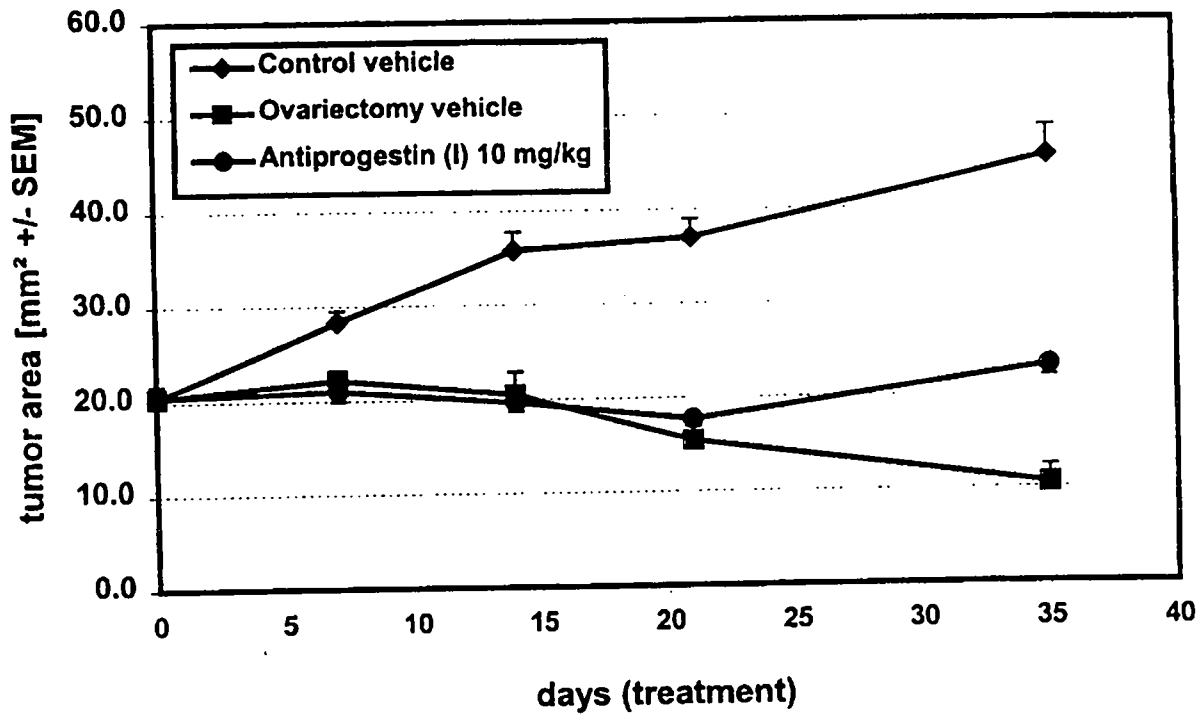
FIG. 4



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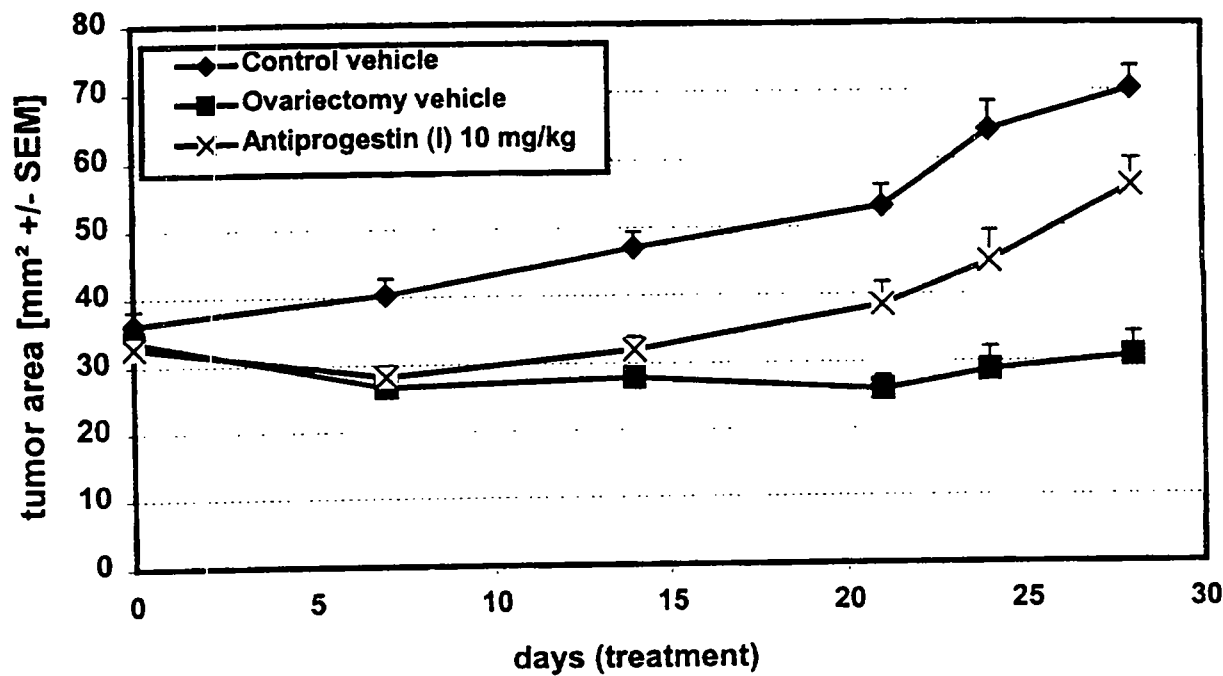
FIG. 5



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FIG. 6



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ABSTRACT

The present invention relates to methods and uses for preventing or treating hormone-dependent disease, in particular breast cancer, in a mammal by antiprogestins, in particular
5 antiprogestin 11β -(4-acetylphenyl)- 17β -hydroxy- 17α -(1,1,2,2,2-pentafluoroethyl)-estra-4,9-dien-3-one or a pharmaceutically acceptable derivative or analogue thereof. The invention further relates to pharmaceutical compositions comprising said antiprogestin.

Oficina Europea de Patentes

Certificado

Los documentos adjuntos son una copia fiel y exacta de la versión original de la solicitud de patente europea que se especifica en la siguiente página.

Solicitud de Patente No.

00250341.5

El Presidente de la Oficina Europea de Patentes

I.L.C. HATTEN-HECKMAN

(Firma y Sello Oficial)

LA HAYA, 28/02/01

Página 2 del Certificado

Solicitud No.: 00250341.5

Fecha de presentación: 18/10/00

Solicitante:

Schering Aktiengesellschaft

13353 Berlín

ALEMANIA

Título de la invención:

Uso de antiprogestinas para la profilaxis y el tratamiento de enfermedades hormona-dependientes

Prioridades reivindicadas: -

Clasificación Internacional de Patentes: -

Países contratantes mencionados en la fecha de presentación:

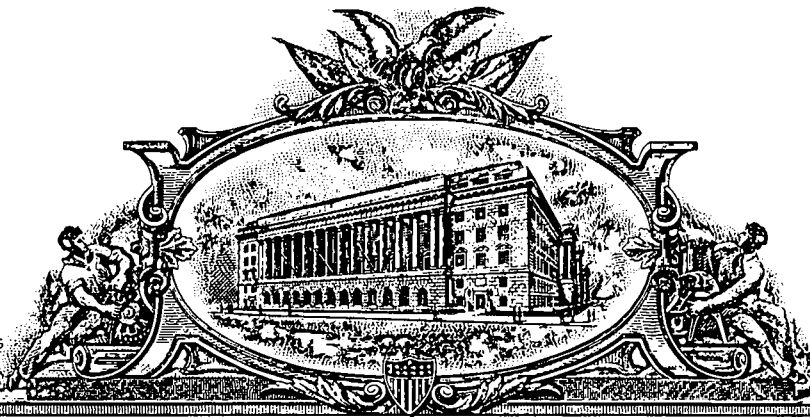
AT/BE/CH/CY/DE/DK/ES/FI/FR/GB/GR/IE/IT/LI/LU/MC/NL/PT/SE/TR

REIVINDICACIONES

1. Uso de la antiprogesterina 11β -(4-acetilfenil)- 17β -hidroxi- 17α -(1,1,2,2,2-pentafluoroetil)-estr-4,9-dien-3-ona o de un derivado o de un análogo de ella farmacéuticamente aceptables para la manufactura de un medicamento para la profilaxis o el tratamiento de una enfermedad hormona-dependiente en un mamífero.
2. Uso de acuerdo con la reivindicación 1, en el cual la enfermedad es cáncer del seno.
3. Uso de acuerdo con la reivindicación 1 o 2, en el cual el mamífero es humano.
4. Uso de acuerdo con cualquiera de las anteriores reivindicaciones, en el cual el medicamento se administra oralmente.
5. Uso de acuerdo con cualquiera de las anteriores reivindicaciones, en el cual la antiprogesterina 11β -(4-acetilfenil)- 17β -hidroxi- 17α -(1,1,2,2,2-pentafluoroetil)-estr-4,9-dien-3-ona se administra en una unidad de dosis de 50 mg.
6. Composición farmacéutica que comprende la antiprogesterina 11β -(4-acetilfenil)- 17β -hidroxi- 17α -(1,1,2,2,2-pentafluoroetil)-estr-4,9-dien-3-ona o un derivado o un análogo de ella farmacéuticamente aceptables en una cantidad suficiente para la profilaxis o el tratamiento de una enfermedad hormona-dependiente en un mamífero.
7. Composición farmacéutica de acuerdo con la reivindicación 6, siendo la enfermedad cáncer de seno.
8. Composición farmacéutica de acuerdo con la reivindicación 6 o 7, siendo el mamífero un humano.
9. Composición farmacéutica de acuerdo con cualquiera de las reivindicaciones 6 a 8, la cual comprende además un antiestrógeno.

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March 04, 2002

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APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A
FILING DATE UNDER 35 USC 111.**

APPLICATION NUMBER: 60/240,998

FILING DATE: *October 18, 2000*

**By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS**



M. Lee

**M. LEE
Certifying Officer**



10/18/00

PROVISIONAL APPLICATION COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION under 37 CFR 1.53(c).

Docket Number SCH-1784-V1

1c916 U.S. PTO
60/240998
10/18/00

INVENTOR(s)/APPLICANT(s)			
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☐ Additional inventors are named on separately numbered sheets attached hereto.

TITLE OF THE INVENTION (280 CHARACTERS MAX)
USE OF ANTIPROGESTINS FOR PROPHYLAXIS AND TREATMENT OF HORMONE-DEPENDENT DISEASES

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ENCLOSED APPLICATION PARTS

☒ Abstract	☐ Small Entity Statement
☒ Specification <i>Number of Pages:</i> 18	<i>Language:</i>
☒ Claims <i>Number of Pages:</i> 1	☐ Other (specify):
☒ Drawing(s) <i>Number of Sheets:</i> 6	

METHOD OF PAYMENT

☒ A check or money order is enclosed to cover the Provisional Filing Fees	PROVISIONAL FILING FEE AMOUNT
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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

- ☒ No.
- ☐ Yes, the name of the U.S. Government agency and the Government contract number are:

Respectfully Submitted,

October 18, 2000

DATE

Anthony J. Zelano

Registration Number 27,969

PROVISIONAL APPLICATION FILING ONLY

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5 **USE OF ANTIPROGESTINS FOR PROPHYLAXIS AND
TREATMENT OF HORMONE-DEPENDENT DISEASES**

Field of the Invention

10 The present invention relates to the use of antiprogestins for the prophylaxis and treatment
of hormone-dependent diseases, in particular breast cancer. The present invention further
relates to pharmaceutical compositions and dosage forms comprising antiprogestins for
the prophylaxis and treatment of hormone-dependent diseases, in particular breast cancer.
A particularly preferred antiprogesterin for use in the invention is the antiprogesterin 11 β -(4-
15 acetylphenyl)-17 β -hydroxy-17 α -(1,1,2,2,2-pentafluoroethyl)-estra-4,9-dien-3-one or a
pharmaceutically acceptable derivative or analogue thereof.

Background of the Invention

20 Endocrine therapy represents a mainstay of effective, minimally toxic, palliative treatment
for metastatic breast cancer. As a standard palliative treatment of non-operable mammary
carcinomas as well as for adjuvant therapy after primary treatment of mammary
carcinomas predominantly the antiestrogen tamoxifen is used. However, tamoxifen cannot
cure breast cancer. Thus, for secondary therapy progestins or aromatase inhibitors are
25 commonly used. In premenopausal women ovariectomy, tamoxifen and LHRH
(luteinizing hormone releasing hormone) analogs achieve comparable results (H.T.
Mouridson et al., *Eur. J. Cancer Clin. Oncol.*, 24, pp. 99-105, 1988).

Although tamoxifen is widely used for adjuvant therapy of breast cancer, its use as a
30 chemopreventive agent is problematic, because it has been shown that the treatment
results in an increase in the incidence of endometrial cancers (I.N. White, *Carcinogenesis*,
20(7):1153-60, 1999).

Antiprogestins represent a relatively new and promising class of therapeutic agents that could have significant impact on breast cancer treatment. Although antiprogestins were originally created with regard to medicinal non-surgical termination of pregnancy (EP 129 499), certain antiprogestins have recently gained importance in the endocrine therapy of those breast cancers involving receptors for progesterone (T. Maudelonde et al., in: J.G.M. Klijn et al., *Hormonal Manipulation of Cancer: Peptides, Growth Factors and New (Anti) Steroidal Agents*, Raven Press, New York, 1987, pp. 55-59). This new strategy in endocrine therapy is based on the antitumor activity of antiprogestins in progesterone receptor-positive human breast cancer cell lines *in vitro* and in several hormone-dependent mammary tumors of the mouse and rat *in vivo*. In particular, the antitumor mechanism of the antiprogestins onapristone and mifepristone (RU 486) was investigated using the hormone-dependent MXT mammary tumor model of the mouse as well as the DMBA- and the NMU-induced mammary tumor models of the rat (M. R. Schneider et al., *Eur. J. Cancer Clin. Oncol.*, Vol. 25, No. 4, pp. 691-701, 1989; H. Michna et al., *Breast Cancer Research and Treatment* 14:275-288, 1989; H. Michna, *J. Steroid. Biochem.* Vol. 34, Nos 1-6, pp. 447-453, 1989). However, due to low activity and adverse side effects involved with e.g. mifepristone this compound could not be recommended as a single agent in the management of breast cancer (D. Perrault et al., *J. Clin. Oncol.* 1996 Oct, 14(10), pp.2709-2712).

Antiprogesterin compounds are suitable for initiating abortions and thus for use in postcoital fertility control, as contraceptives for women (WO-A 93/23020, WO-A 93/21927) and further for the treatment of hormone irregularities, for initiating menstruation and for initiating labor. Further indications are in the field of hormone substitution therapy (WO-A 94/18983), the treatment of afflictions related to dysmenorrhea and the treatment of endometriosis (EP-A 0 266 303) as well as myomas.

17 α -fluoroalkylsteroids having strong antiprogesterin activity as well as methods for producing them are described in WO 98/34947.

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Antiprogestins of the prior art tested or used previously due to their antitumor activity frequently exhibited certain disadvantages.

- For example, despite the fact that prior art antiprogestins exhibited antigestagenic activity, these compounds were not suitable treatments for hormone-dependent diseases such as breast cancer. In particular, prior art compounds were associated with side effects, e.g. mifepristone exhibits strong antiglucocorticoid side effects (cf. L.M. Kettel et al., *Fertil. Steril.* 1991 Sep, 56(3), pp. 402-407; X. Bertagna, *Psychoneuroendocrinology* 1997; 22 Suppl. 1, pp. 51-55) and besides it showed only moderate activity in clinical trials (see again D. Perrault et al., *J. Clin. Oncol.* 1996 Oct, 14(10), pp.2709-2712). Regarding side effects of other hormone-based therapies, as already mentioned above, tamoxifen administration can result in an increase in the incidence of endometrial cancers (I.N. White, *Carcinogenesis*, 20(7):1153-60, 1999).
- Another problem with prior art antiprogestins was poor bioavailability when administered orally. Thus, they generally had to be administered in high doses, giving rise to possible unfavorable side effects. Moreover, oral administration is desirable with respect to patient convenience and compliance.
- Furthermore, there is still a need for compounds that are active not only in the treatment, but also in the prophylaxis of breast cancer and other hormone-dependent diseases. The increased incidence of endometrial cancer associated with tamoxifen tends to show that this compound is unsuitable for prophylaxis treatment of healthy women, and no other suitable compounds are available (cf. L. Bergman et al., *The Lancet*, Vol. 356, Sept. 9, 2000; 881-887).

Object of the Present Invention

- It is an object of the present invention to prevent or reduce the disadvantages of the prior art methods for preventing or treating hormone-dependent diseases, such as breast cancer.

It is especially desired that a means of preventing and treating hormone-dependent diseases, such as breast cancer, via the administration of highly effective agents is provided that is superior to known methods and agents, including ovariectomy. Thus it is further especially desired to provide a treatment of hormone-dependent diseases, such as breast cancer, that prevents serious and risk-laden surgery involved with ovariectomy. It is further desired to provide an agent for use according to the invention exhibiting less side effects than previously known or suggested methods for treating and preventing hormone-dependent diseases such as breast cancer.

- 10 It is a further object of the present invention to provide pharmaceutical compositions comprising highly effective antitumor agents for the prophylaxis and treatment of breast cancer and other hormone-dependent diseases.

These objects are surprisingly achieved by the use of antiprogestins according to the present invention and by pharmaceutical compositions and dosage forms comprising such antiprogestins. Particularly preferred in this regard is the antiprogesterin 11 β -(4-acetylphenyl)-17 β -hydroxy-17 α -(1,1,2,2,2-pentafluoroethyl)-estra-4,9-dien-3-one or a pharmaceutically acceptable derivative or analogue thereof.

- 20 It is a further object of the present invention to provide antiprogestins, such as the antiprogesterin 11 β -(4-acetylphenyl)-17 β -hydroxy-17 α -(1,1,2,2,2-pentafluoroethyl)-estra-4,9-dien-3-one or pharmaceutically acceptable derivatives or analogues thereof, that are particularly suitable for oral administration.

25 Summary of the Invention

- The present invention is based on the novel and unexpected observation that certain antiprogestins, in particular 11 β -(4-acetylphenyl)-17 β -hydroxy-17 α -(1,1,2,2,2-pentafluoroethyl)-estra-4,9-dien-3-one or a pharmaceutically acceptable derivative or analogue thereof, are exceptionally active in the prevention and reduction of tumor growth in DMBA (7,12-dimethylbenzanthracene)- and NMU (N-methylnitrosourea)-induced breast cancer models. In fact, the antiprogesterin 11 β -(4-acetylphenyl)-17 β -hydroxy-17 α -

(1,1,2,2,2-pentafluoroethyl)-estra-4,9-dien-3-one (I) turned out to be distinctly more potent than tamoxifen and ovariectomy in the prevention of breast cancer development.

Thus, the present invention provides a method for prophylaxis and treatment of breast cancer and other hormone-dependent diseases in mammals, in particular humans, in need of such treatment, said method comprising administering a pharmaceutically effective amount of an antiprogesterin, in particular 11β -(4-acetylphenyl)- 17β -hydroxy- 17α -(1,1,2,2,2-pentafluoroethyl)-estra-4,9-dien-3-one, or a pharmaceutically acceptable derivative thereof or analogue thereof, to a patient.

The present invention further provides pharmaceutical compositions comprising an antiprogesterin, in particular 11β -(4-acetylphenyl)- 17β -hydroxy- 17α -(1,1,2,2,2-pentafluoroethyl)-estra-4,9-dien-3-one or a pharmaceutically acceptable derivative or analogue thereof, in an amount sufficient for the prophylaxis or treatment of breast cancer or other hormone-dependent diseases.

The preferred antiprogesterin 11β -(4-acetylphenyl)- 17β -hydroxy- 17α -(1,1,2,2,2-pentafluoroethyl)-estra-4,9-dien-3-one will hereinafter be referred to as "antiprogesterin (I)".

Brief Description of the Figures

Figure 1 shows the tumor development prevention effect of antiprogesterin (I) in the DMBA-induced mammary carcinoma of the rat, compared with a control, tamoxifen and ovariectomy.

Figure 2 shows the tumor growth inhibiting effects of antiprogesterin (I) in a dose-response study in the DMBA-induced mammary carcinoma of the rat, compared with a control, the antiprogesterin onapristone as well as ovariectomy. The study was performed with 0.5, 2.0, 5.0 and 10.0 mg/kg s.c. doses of antiprogesterin (I).

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Figure 3 shows the tumor development prevention effect of antiprogesterin (I) in the NMU-induced mammary carcinoma of the rat, compared with a control, the antiestrogens raloxifen and tamoxifen, the aromatase inhibitor letrozol as well as ovariectomy.

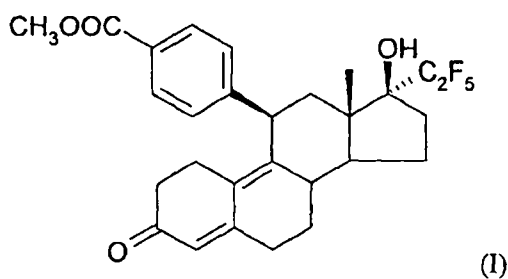
- 5 Figure 4 shows the tumor growth inhibiting effect of 0.5 and 1.0 mg/kg doses of antiprogesterin (I) in the NMU-induced mammary carcinoma of the rat, compared with a control, onapristone (5 mg/kg) and ovariectomy.

- 10 Figure 5 shows the tumor growth inhibiting effect of antiprogesterin (I) in a 10 mg/kg s.c. dose in the T47D human xenograft in scid mice, compared to a control as well as ovariectomy.

- 15 Figure 6 shows the tumor growth inhibiting effect of antiprogesterin (I) in a 10 mg/kg s.c. dose in the MCF7 human xenograft in scid mice, compared to a control as well as ovariectomy.

Detailed Description of the Invention

- 20 Antiprogesterin (I) — 11 β -(4-acetylphenyl)-17 β -hydroxy-17 α -(1,1,2,2,2-pentafluoroethyl)-estra-4,9-dien-3-one — is represented below by formula (I):



- 25 Antiprogesterin (I) (or a pharmaceutically acceptable derivative or analogue thereof having comparable activity) is a valuable pharmaceutical agent having strong antiprogesterin activity. Antiprogesterin (I), as well as further antiprogesterins, can be used according to the

present invention for the prophylaxis and treatment of breast cancer and other hormone-dependent diseases.

5 The term "antiprogesterone" in the context of the present invention is intended to primarily comprise all compounds being capable of competitively inhibiting progesterone receptors. However, it should also encompass compounds capable of inhibiting the biosynthesis of progestins.

10 A pharmaceutically acceptable derivative or analogue of antiprogesterone (I) in the context of the present invention may include, for example, any one of the inventive compounds disclosed in WO 98/34947.

15 The term "hormone-dependent diseases" in the context of the present invention may include, but is not limited to, breast cancer, ovarian cancer, endometrial cancer, myeloma, anovulatory infertility, meningoma, i.e. diseases which substantially originate or are influenced by the presence of hormone receptors and/or hormone-dependent pathways.

20 As regards the superiority of the present invention over the prior art, it is especially favorable that, e.g., in antiprogesterone (I) used according to the present invention further endocrine side effects, such as e.g. androgen, estrogen or antiglucocorticoid activity are only very weak, if present at all. Due to the high bioavailability of antiprogesterone (I) it can be administered orally, thus rendering the treatment for a patient in need thereof as convenient as possible. As a further favorable consequence, antiprogesterone (I) is well tolerated and can be administered in relatively low doses compared to established
25 treatments thus reducing undesirable side effects, such as an increase in the incidence of endometrial cancers with the administration of tamoxifen (see I.N. White, *Carcinogenesis*, 20(7):1153-60, 1999; L. Bergman et al., *The Lancet*, Vol. 356, Sept. 9, 2000, 881-887) as well as the antiglucocorticoid effects and certain toxic side effects related to the administration of mifepristone (see D. Perrault et al., *J. Clin. Oncol.* 1996 Oct, 14(10),
30 pp.2709-2712; L.M. Kettel et al., *Fertil. Steril.* 1991 Sep, 56(3), pp.402-407; X. Bertagna, *Psychoneuroendocrinology* 1997, 22 Suppl. 1; pp. 51-55).

A further advantage of the present invention over the prior art is the provision of an effective method for the prophylaxis of hormone-dependent diseases such as breast cancer, such that patients under high risk of developing or re-developing hormone-
5 dependent diseases can be treated in advance to avoid incidence of such diseases.

In a first aspect the present invention relates to a method for the prophylaxis or treatment of breast cancer and other hormone-dependent diseases, comprising administering at least one antiprogesterin, preferably antiprogesterin (I) or a pharmaceutically acceptable derivative
10 or analogue thereof to a mammal, preferably a human, in need of such prophylaxis or treatment.

In a further aspect the present invention relates to the use of antiprogesterins as defined above, preferably antiprogesterin (I) or a pharmaceutically acceptable derivative or analogue
15 thereof, for the manufacture of a medicament, in particular for the prophylaxis or treatment of breast cancer or other hormone-dependent diseases.

In another aspect the present invention relates to pharmaceutical compositions comprising at least one antiprogesterin as defined above, preferably antiprogesterin (I) or a
20 pharmaceutically acceptable derivative or analogue thereof. Optionally the antiprogesterin (I) can be combined with other pharmacologically active agents. For example, the antiprogesterin may also be combined with a cytotoxic agent for treatment by coupling to a hormone receptor.

25 The manufacture of the medicaments may be performed according to methods known in the art. Commonly known and used adjuvants as well as further suitable carriers or diluents may be used. Suitable carriers and adjuvants may be such as recommended for pharmacy, cosmetics and related fields in: *Ullmann's Encyclopedia of Technical Chemistry*, Vol. 4, (1953), pp. 1-39; *Journal of Pharmaceutical Sciences*, Vol. 52 (1963),
30 p. 918ff; H.v.Czetsch-Lindenwald, "Hilfsstoffe für Pharmazie und angrenzende Gebiete";

Pharm. Ind. 2, 1961, p.72ff; Dr. H.P. Fiedler, *Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete*, Cantor KG, Aulendorf in Württemberg, 1971.

Antiprogestins suitable for the purposes of the present invention, preferably antiprogestin
5 (I) or a pharmaceutically acceptable derivative or analogue thereof, can be incorporated into pharmaceutical compositions according to known methods of preparing galenics for oral or parenteral, e.g., intraperitoneal, intramuscular, subcutaneous or percutaneous application. They can also be implanted into tissue. Implants can comprise as inert materials e.g. biologically degradable polymers or synthetic silicones such as e.g. silicone
10 rubber.

They can be administered in the form of tablets, pills, dragees, gel capsules, granules, suppositories, implants, injectable sterile aqueous or oily solutions, suspensions or emulsions, ointments, creams, gels or by intravaginal (e.g., vaginal rings) or intrauterine
15 systems (e.g., diaphragms, loops).

For the preparation of pharmaceutical compositions for oral administration, the antiprogestins suitable for the purposes of the present invention as defined above can be admixed with commonly known and used adjuvants and carriers such as for example, gum
20 arabic, talcum, starch, sugars such as, e.g., mannitose, methyl cellulose, lactose, gelatin, surface-active agents, magnesium stearate, aqueous or non-aqueous excipients, paraffin derivatives, cross-linking agents, dispersants, emulsifiers, lubricants, conserving agents and flavoring agents (e.g., ethereal oils). In the pharmaceutical composition, the antiprogestin may be dispersed in a microparticle, e.g. a nanoparticulate, composition.

25 In order to further enhance the bioavailability of the active agent, the antiprogestins suitable for the purposes of the present invention as defined above can also be formulated as cyclodextrin clathrates by reacting them with α -, β - or γ -cyclodextrines or derivatives thereof according to the method as disclosed in PCT/EP95/02656.

30 For parenteral administration the antiprogestins suitable for the purposes of the present invention as defined above can be dissolved or suspended in a physiologically acceptable

diluent, such as, e.g., oils with or without solubilizers, surface-active agents, dispersants or emulsifiers. As oils for example and without limitation, olive oil, peanut oil, cottonseed oil, soybean oil, castor oil and sesame oil may be used.

- 5 The amount to be administered (i.e., a "pharmaceutically effective amount") varies within a broad range and depends on the condition to be treated and the mode of administration. It can cover any amount efficient for the intended treatment. Determining a "pharmaceutically effective amount" is within the purview of the person skilled in the art.
- 10 One unit dose may represent about 0.1 to 100 mg active agent(s). For administration to humans, the daily dose of the active agent(s) is about 0.1 to 400 mg, preferably 10 to 100 mg, most preferably 50 mg.

- The pharmaceutical compositions according to the present invention can also be
- 15 administered via a depot injection, an implant preparation or an IUD (internal uterine device), optionally for sustained delivery of the active agent(s).

- The preferred mode of administration is oral administration. The antiprogesterins for use according to the invention, and in particular, antiprogesterin (I) or a pharmaceutically
- 20 acceptable derivative or analogue thereof are particularly suitable for oral administration.

- According to all aspects of the present invention it is also possible to combine at least one antiprogesterin as defined above, in particular antiprogesterin (I) or a pharmaceutically acceptable derivative or analogue thereof, with at least one antiestrogen, because many
- 25 hormone-dependent diseases, in particular breast cancer, exhibit not only progesterone receptors, but also estrogen receptors. The antiestrogen may be administered either simultaneously with or sequentially to the antiprogesterin, and in particular with/to antiprogesterin (I) or a pharmaceutically acceptable derivative or analogue thereof. The amount of antiprogesterin and antiestrogen may be equal or one component may be more
- 30 predominant than the other, such as in an antiprogesterin:antiestrogen ratio of 1:50 to 50:1, preferably 1:30 to 30:1, and most preferably 1:15 to 15:1.

Examples of suitable antiestrogens for use according to the invention are non-steroidal antiestrogens, such as tamoxifen and nafoxidine as well as raloxifen, and EM800 and the steroidal antiestrogen faslodex. Examples of steroidal antiestrogens include those
5 disclosed in EP 0 348 341 A and those disclosed in WO 98/07740, in particular, 11 β -
flouro-7 α -{5-[N-methyl-N-3-(4,4,5,5,5-pentafluoropentylthio-propylamino)-pentyl]}-
estra-1,3,5(10)-trien-3,17 β -diol, or those disclosed in WO 99/33855, in particular 11 β -
flouro-7 α -{5-[methyl-(7,7,8,8,9,9,10,10,10-nonafluoro-decyl)-amino]-pentyl}-estra-
1,3,5(10)-trien-3,17 β -diol or pharmaceutically acceptable derivatives or analogues
10 thereof. Aromatase inhibitors having an antiestrogenic effect, such as those disclosed on
pages 7 to 8 of EP 0 495 825 B1 may also be used as antiestrogens.

The invention is further illustrated in the examples. The following examples are not to be understood as a limitation.

Examples

Example 1:

DMBA-induced breast cancer model in rat (prevention experiment)

Materials and Methods:

Immature female Sprague-Dawley rats (49 - 51 days old; 10 animals/group) were used in this study. The carcinogen 7,12-dimethylbenz[a]anthracene (DMBA) was given as a
25 single oral administration (10 mg). Treatment was started 20 days later as followed: 1)
solvent control, 2) ovariectomy at treatment start, 3) tamoxifen, 1 mg/kg s.c., 4)
antiprogesterin (I), 3 mg/kg, s.c., 6 days/week. Rats were examined weekly for breast
tumors by palpation. As a parameter for the prophylactic effect the tumor incidence
(number of animals/group with tumors in %) was determined. For a further description
30 and evaluation of DMBA and NMU prevention models, see R.G. Metha, *European
Journal of Cancer* 36 (2000), pp. 1275-1282.

Results:

5 In the control group all rats developed mammary tumors within 10 weeks after treatment
start (incidence 100%) and progressive tumor growth was observed. Prophylactic
treatment with the antiprogesterone (I) prevented the tumor development for 12 weeks
completely, and at the end of the experiment, after 22 weeks, in only one rat a tumor was
detected (incidence 10%). After ovariectomy at the end of the experiment 40% of the rats
had developed tumors. In comparison, treatment with the antiestrogen tamoxifen reduced
10 the tumor incidence only to 60% (see fig. 1)

Conclusion:

15 In the DMBA-induced mammary tumor model in the rat, the antiprogesterone (I) completely
suppressed the tumor development in intact animals for more than 12 weeks after
treatment start. Figure 1 clearly shows the superiority in activity of antiprogesterone (I) over
the conventional anti-breast cancer reagent tamoxifen and even over standard estrogen
deprivation therapy (ovariectomy) with respect to prophylactic treatment. Antiprogesterone
(I) is thus superior to the established standard therapy for preventing breast cancer in
20 women under high risk of developing the disease (tamoxifen prophylactic therapy).

These and the following results indicate that the use of antiprogesterone (I) for the
prophylaxis and treatment of breast cancer is superior to established standard treatments.

25 Example 2:

DMBA-induced breast cancer model in rat (therapy experiment/dose-response study)

Materials and Methods:

30 Immature female Sprague-Dawley rats (49 - 51 days old; 10 animals/group) were used in
this study. Mammary tumors were induced by a single oral administration of 10 mg 7,12-
dimethylbenz[a]anthracene (DMBA, Serva/Heidelberg). Rats with at least one established

tumor with a size of more than 150 mm² were treated for 4 weeks by: 1) solvent control, 2) ovariectomy at treatment start, 3) antiprogesterin (I), 0,5 mg/kg s.c., 4) antiprogesterin (I), 2 mg/kg s.c., 5) antiprogesterin (I), 5 mg/kg s.c., 6) antiprogesterin (I), 10 mg/kg s.c., and 7) onapristone, 5 mg/kg, s.c., daily. As a parameter for growth inhibition the change of tumor area (in % with respect to initial tumor size) determined by weekly caliper measurements was used. For statistical analysis of intergroup differences of mean values the Kruskal-Wallis-test was used.

Results:

10

In intact control animals, progressive tumor growth was observed, whereas ovariectomy caused a considerable tumor regression in 90% of the animals. Treatment with antiprogesterin (I) at doses of or above 2 mg/kg resulted in a significant inhibition of tumor growth compared with the control (see fig. 2). There was a clear dose-response relationship. Whereas treatment with 0.5 mg/kg antiprogesterin (I) did not significantly prevent the tumor from growing, at 2 mg/kg maximal growth inhibition was observed. In this group a complete tumor regression was seen in 50% of the rats. The effect of the highest dose of antiprogesterin (I) tested in this experiment (10 mg/kg), was comparable to that of 2 mg/kg. Onapristone (5 mg/kg, s.c.) was distinctly less effective than antiprogesterin (I) at comparable doses.

20

Conclusion:

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In the DMBA-induced mammary tumor model in the rat, antiprogesterin (I) completely suppresses the tumor growth in intact animals. It was found that 2 mg/kg antiprogesterin (I) has a maximal effect on tumor growth. Antiprogesterin (I) was distinctly superior to onapristone.

30

Example 3:NMU-induced breast cancer model in rat (prevention experiment)

Materials and Methods:

5

Tumors were induced by a single intravenous injection of NMU (nitrosomethylurea, 50 mg/kg) in female Sprague-Dawley rats (obtained from Tierzucht Schönwalde, age 50-55 days). Treatment was started 10 days later as followed: 1) solvent control, 2) ovariectomy at treatment start, 3) tamoxifen, 3 mg/kg s.c., 4) antiprogesterin (I), 3 mg/kg, s.c., 5) letrozole, 3 mg/kg s.c., 6) raloxifen, 3 mg/kg s.c., 6 days/week. Rats were examined weekly for breast tumors by palpation. As a parameter for the prophylactic effect the tumor incidence (number of animals/group with tumors in %) was determined. For a further description and evaluation of DMBA and NMU prevention models, see R.G. Metha, *European Journal of Cancer* 36 (2000), pp. 1275-1282.

15

Results:

In the control group all rats developed mammary tumors within 10 weeks after treatment start (incidence 100%; see fig. 3) and progressive tumor growth was observed.

20 Prophylactic treatment with the antiprogesterin (I) prevented the tumor development for 12 weeks completely, and at the end of the experiment, after 27 weeks, in only one rat a tumor was detected (incidence 10%). In comparison, in treatment with the other antiestrogens or the aromatase inhibitor letrozole the tumor incidence was reduced only to 20 - 60%. After ovariectomy at the end of the experiment 20% of the rats had developed tumors.

25

Conclusion:

In the NMU-induced mammary tumor model in the rat, antiprogesterin (I) completely
30 suppressed the tumor development in intact animals for more than 12 weeks after treatment start. The effect of the prophylactic treatment by antiprogesterin (I) was superior

to that of conventional antiestrogens for breast cancer therapy (i.e., raloxifen, tamoxifen) and aromatase inhibitor letrozol and to standard estrogen deprivation therapy (ovariectomy) regarding tumor incidence and tumor growth.

- 5 As in the DMBA-induced tumor model (see Example 1), these results indicate that antiprogesterin (I) effectively prevents the development of breast tumors in a manner which is superior to the standard prophylactic treatment, e.g. with tamoxifen.

10 Example 4:

NMU-induced breast cancer model in rat (therapy experiment)

Materials and Methods:

- 15 Tumors were induced by a single intravenous injection of NMU (nitrosomethylurea, 50 mg/kg) in female Sprague-Dawley rats (obtained from Tierzucht Schönwalde, age 50-55 days). Starting 10 days later, rats with at least one established tumor were treated for 4 weeks by: 1) solvent control, 2) ovariectomy at treatment start, 3) antiprogesterin (I), 1.0 mg/kg/day, 4) antiprogesterin (I), 0.5 mg/kg/day and 5) onapristone, 5 mg/kg/day. As a
20 parameter for growth inhibition the change of tumor area (in % of initial tumor size) determined by weekly caliper measurements was used. For statistical analysis of intergroup differences of mean values the Kruskal-Wallis-test was used.

Results:

- 25 In intact control animals, progressive tumor growth was observed, whereas ovariectomy caused a complete tumor growth inhibition. Treatment with antiprogesterin (I) at doses of 0.5 or 1.0 mg/kg resulted in a significant inhibition of tumor growth compared with the control (see fig. 4). Onapristone (5 mg/kg) was distinctly less effective than antiprogesterin
30 (I) at the much lower dose of 0.5 mg/kg.

Conclusions:

In the MNU-induced mammary tumor model in the rat, antiprogesterin (I) completely suppresses the tumor growth in intact animals. It was found that at a dose of 1.0 mg/kg and even at a dose of only 0.5 mg/kg antiprogesterin (I) has a significant effect on tumor growth. Thus, antiprogesterin (I) was superior to known antiprogesterins like onapristone.

Example 5:

10 T47D Human xenograft (therapy experiment)

Materials and Methods:

Female Fox Chase scid mice (M&B) were supplemented with estradiol pellets (Innovative Research of America). T47D breast cancer cells, obtained from cell culture and suspended in matrigel, were implanted s.c. in the inguinal region of the mice. Treatment was started when the tumors were approximately 25 mm² in size. Treatment was continued until progression of the tumors. Experimental groups were: 1) control (vehicle), 2) ovariectomy, 3) antiprogesterin (I), 10 mg/kg s.c.. Tumor area was determined by caliper measurements. The Kruskal Wallis test was used for statistical analysis of intergroup differences of mean values.

Results:

In the T47D breast cancer model, ovariectomy resulted in a considerable inhibition of tumor growth, compared with the rapid growth in the control. Fig. 5 shows that the s.c. application of 10 mg/kg antiprogesterin (I) also caused an inhibition of tumor growth, almost comparable to the effect of conventional estrogen deprivation therapy (ovariectomy).

Conclusion:

The effect of antiprogesterin (I) in inhibiting the growth of the human T47D breast cancer xenografted in Fox Chase scid mice is comparable to the effect of standard estrogen deprivation therapy (ovariectomy) which is considered to be the maximum effective method of inhibiting growth of breast cancer in this model.

Example 6:

MCF7 Human xenograft (therapy experiment)

Materials and Methods:

Female Fox Chase scid mice (M&B) were supplemented with estradiol pellets (Innovative Research of America). MCF7 breast cancer cells, obtained from cell culture and suspended in matrigel, were implanted s.c. in the inguinal region of the mice. Treatment was started when the tumors were approximately 25 mm² in size. Treatment was continued until progression of the tumors. Experimental groups were: 1) control (vehicle), 2) ovariectomy, 3) antiprogesterin (I), 10 mg/kg s.c. Tumor area was determined by caliper measurements. The Kruskal Wallis test was used for statistical analysis of intergroup differences of mean values.

Results:

In the MCF7 breast cancer model, ovariectomy resulted in a considerable inhibition of tumor growth, compared with the rapid growth in the control. Fig. 6 shows that the s.c. application of 10 mg/kg antiprogesterin (I) also caused an inhibition of tumor growth, almost comparable to the effect of conventional estrogen deprivation therapy (ovariectomy).

Conclusion:

- The effect of antiprogesterin (I) in inhibiting the growth of the human MCF7 breast cancer xenografted in Fox Chase scid mice is comparable to the effect of standard estrogen deprivation therapy (ovariectomy) which is considered to be the maximum effective method of inhibiting growth of breast cancer in this model.
- 5

CLAIMS

1. Method for treating a hormone-dependent disease in a mammal comprising administering a pharmaceutically effective amount of the antiprogesterin 11 β -(4-acetylphenyl)-17 β -hydroxy-17 α -(1,1,2,2,2-pentafluoroethyl)-estr-4,9-dien-3-one
5 or a pharmaceutically acceptable derivative or analogue thereof to a patient in need of such treatment.
2. The method according to claim 1, wherein the disease is breast cancer.
10
3. The method according to claim 1, wherein the mammal is a human.
4. The method according to claim 1, wherein the medicament is administered orally.
- 15 5. The method according to claim 1, wherein the antiprogesterin 11 β -(4-acetylphenyl)-17 β -hydroxy-17 α -(1,1,2,2,2-pentafluoroethyl)-estr-4,9-dien-3-one is administered in a unit dose of 50mg.
- 20 6. Pharmaceutical composition comprising the antiprogesterin 11 β -(4-acetylphenyl)-17 β -hydroxy-17 α -(1,1,2,2,2-pentafluoroethyl)-estra-4,9-dien-3-one or a pharmaceutically acceptable derivative or analogue thereof in an amount sufficient for the prophylaxis or treatment of a hormone-dependent disease in a mammal.
- 25 7. Pharmaceutical composition according to claim 6, wherein the disease is breast cancer.
8. Pharmaceutical composition according to claim 6, wherein the mammal is a human.
- 30 9. Pharmaceutical composition according to claim 6 further comprising an antiestrogen.

ABSTRACT

The present invention relates to methods and uses for preventing or treating hormone-dependent disease, in particular breast cancer, in a mammal by antiprogestins, in particular
5 antiprogestin 11β -(4-acetylphenyl)- 17β -hydroxy- 17α -(1,1,2,2,2-pentafluoroethyl)-estra-4,9-dien-3-one or a pharmaceutically acceptable derivative or analogue thereof. The invention further relates to pharmaceutical compositions comprising said antiprogestin.

FIG. 1

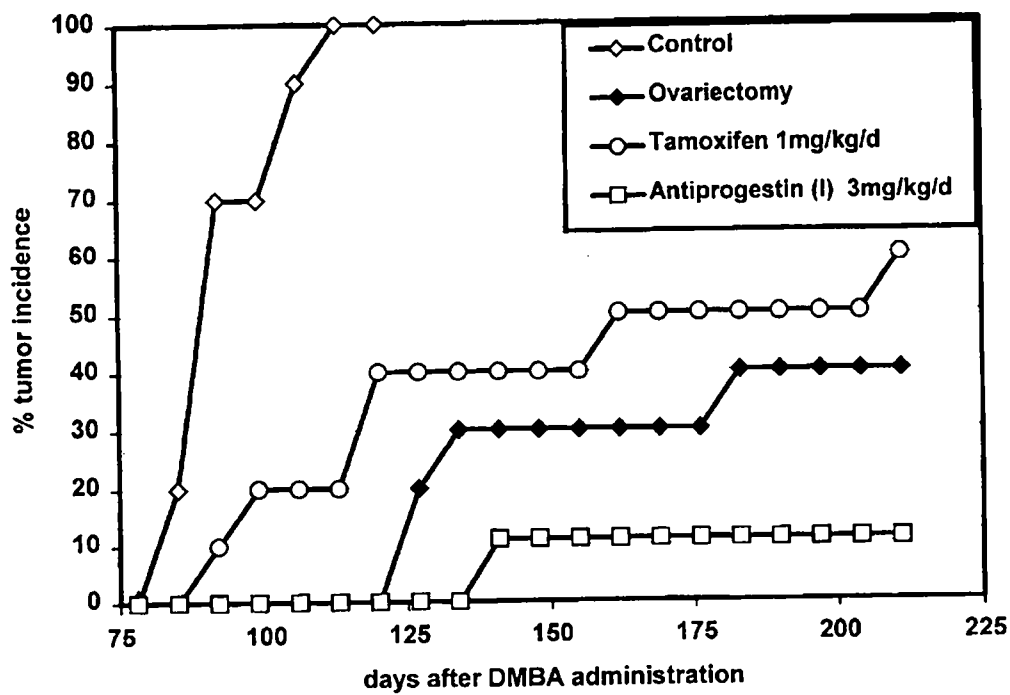


FIG. 2

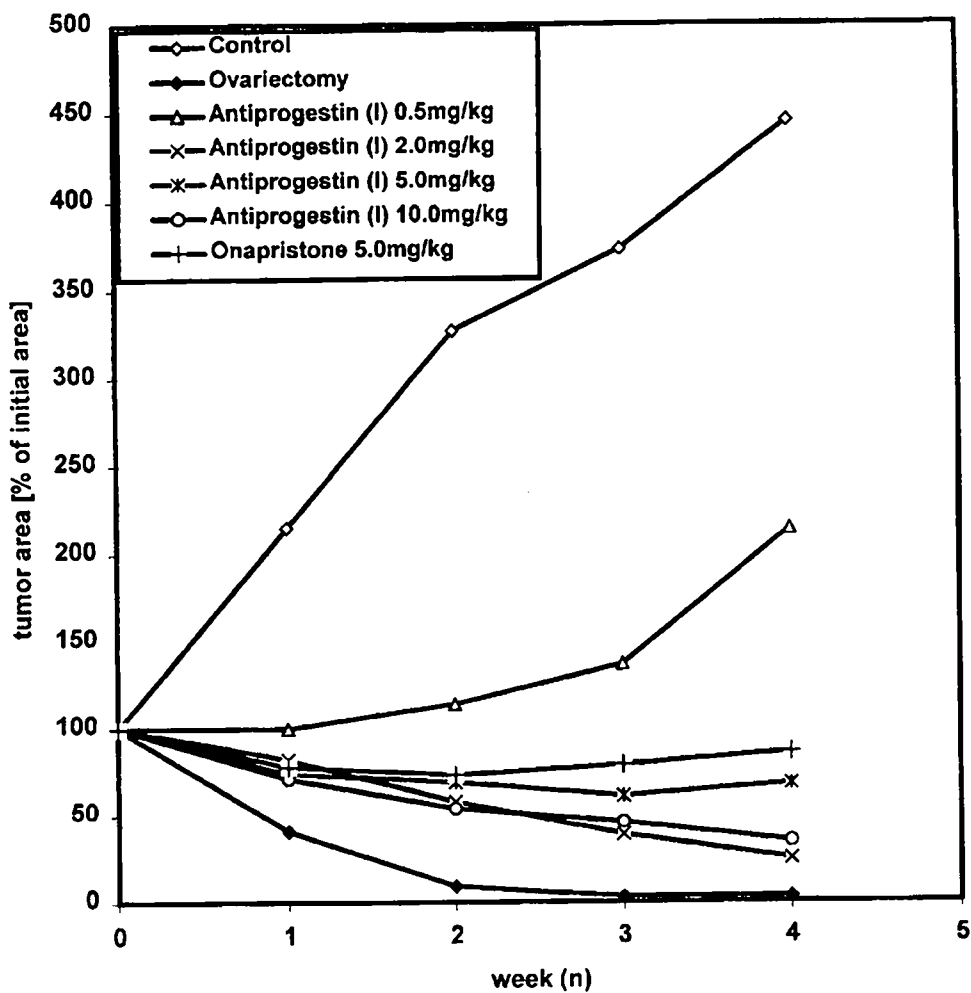


FIG. 3

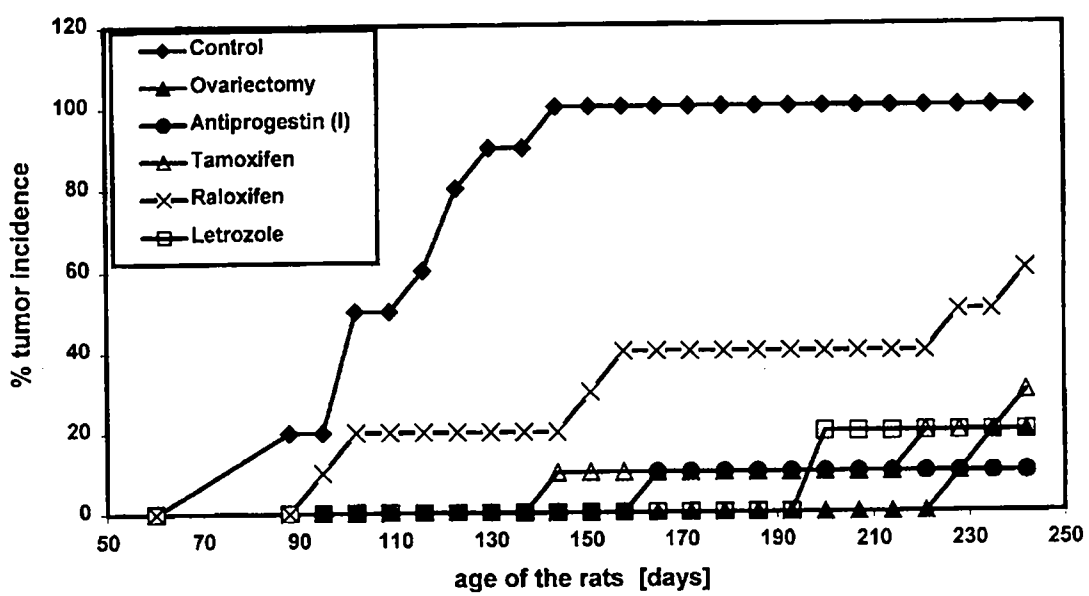


FIG. 4

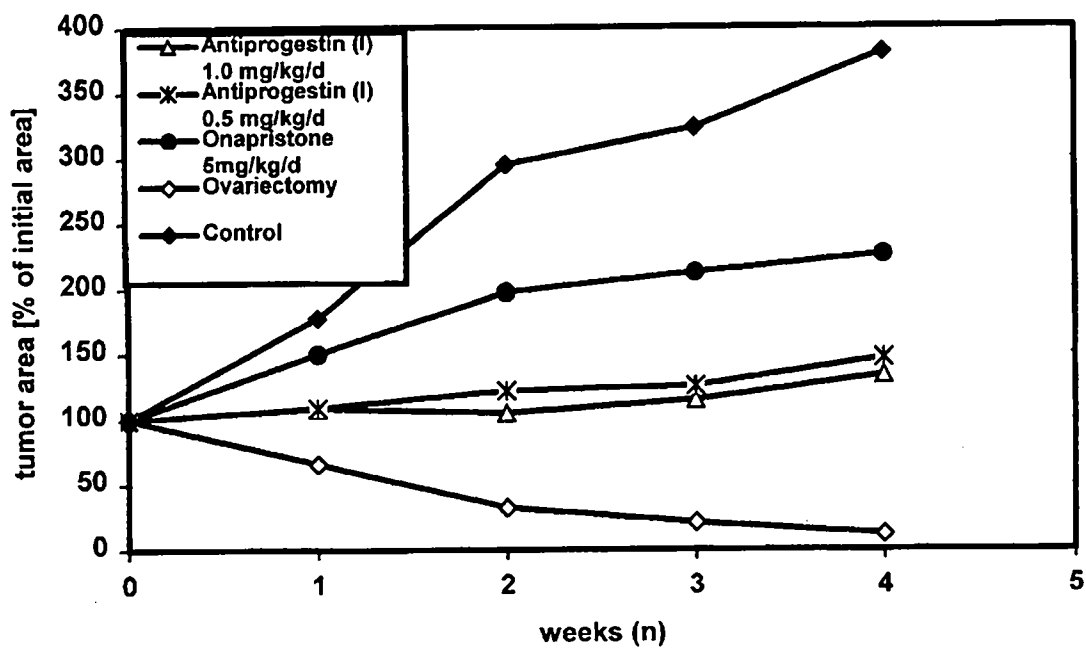


FIG. 5

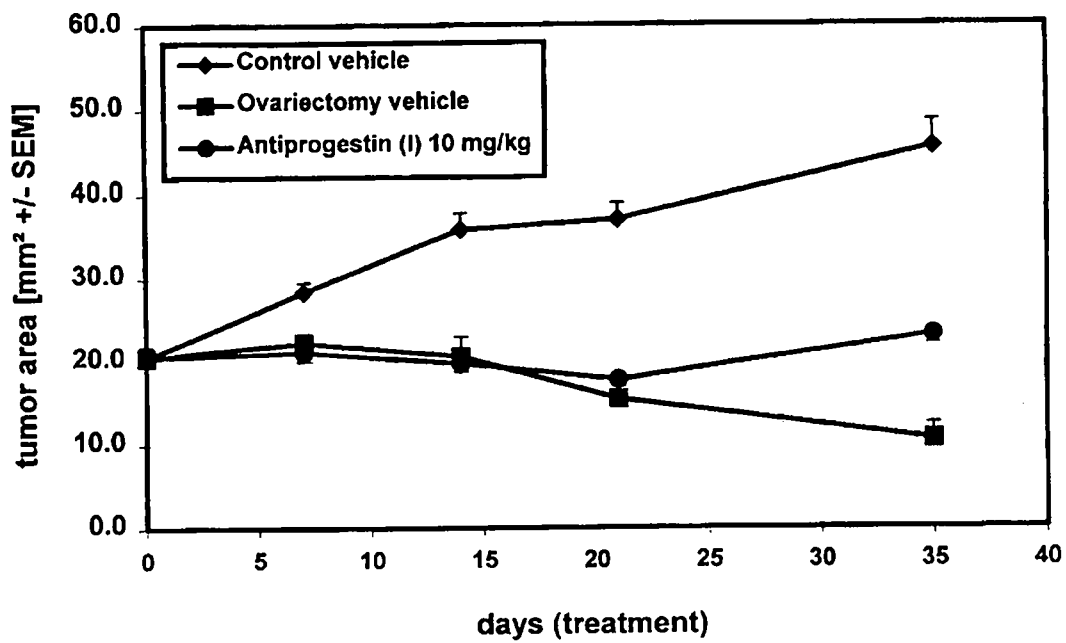
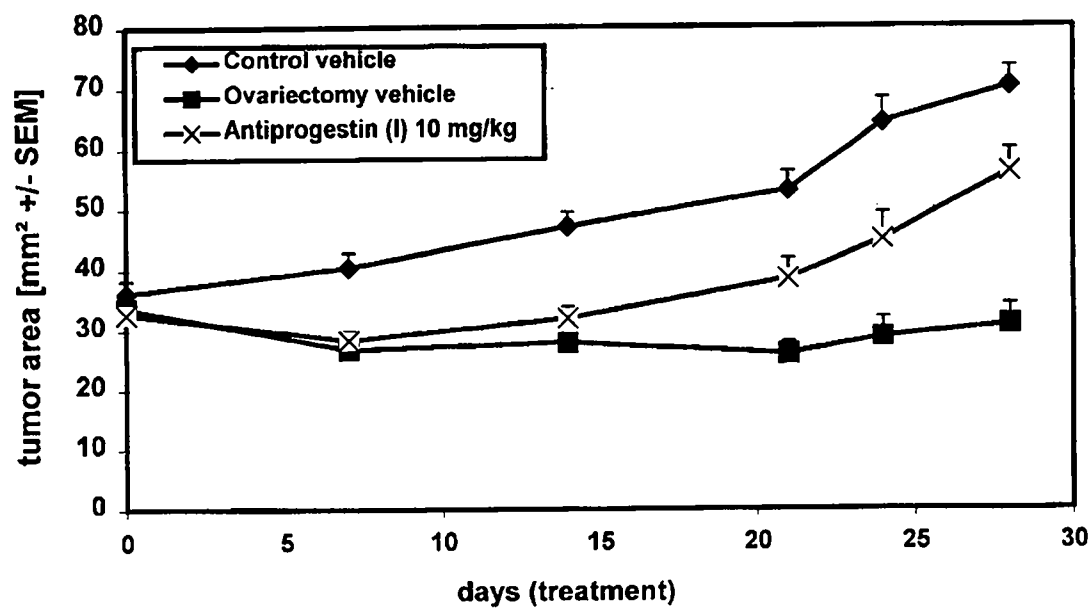


FIG. 6



LOS ESTADOS UNIDOS DE AMERICA

A TODOS CUANTOS LAS PRESENTES VIEREN:

DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS

Oficina de Patentes y Marcas de los Estados Unidos

Marzo 04 del 2002

SE CERTIFICA QUE ADJUNTO SE ENCUENTRA UNA COPIA FIEL Y EXACTA DE LOS REGISTROS DE LA OFICINA DE PATENTES Y MARCAS DE LOS ESTADOS UNIDOS RESPECTO A LOS DOCUMENTOS DE LA SOLICITUD DE PATENTE IDENTIFICADA ABAJO, LA CUAL CUMPLIO CON LOS REQUISITOS PARA QUE SE LE OTORGARA UNA FECHA DE PRESENTACION DE CONFORMIDAD CON 35 USC 111.

SOLICITUD NUMERO: 60/240,998

FECHA DE PRESENTACION: *Octubre 18 del 2000*

Por Autoridad del

COMISIONADO DE PATENTES Y MARCAS

M. LEE, Funcionario de Certificaciones

(Firma y Sello Oficial)

REIVINDICACIONES

1. Método para el tratamiento de una enfermedad hormona-dependiente en un mamífero, método que comprende administrar una cantidad farmacéuticamente eficaz de la antiprogestina 11β -(4-acetilfenil)- 17β -hidroxi- 17α -(1,1,2,2,2-pentafluoroetil)-estr-4,9-dien-3-ona o un derivado o un análogo de ella farmacéuticamente aceptables a un paciente que necesite dicho tratamiento.
2. El método de acuerdo con la reivindicación 1, en el cual la enfermedad es cáncer del seno.
3. El método de acuerdo con la reivindicación 1, en el cual el mamífero es humano.
4. El método de acuerdo con la reivindicación 1, en el cual el medicamento se administra oralmente.
5. El método de acuerdo con la reivindicación 1, en el cual la antiprogestina 11β -(4-acetilfenil)- 17β -hidroxi- 17α -(1,1,2,2,2-pentafluoroetil)-estr-4,9-dien-3-ona se administra en una unidad de dosis de 50 mg.
6. Composición farmacéutica que comprende la antiprogestina 11β -(4-acetilfenil)- 17β -hidroxi- 17α -(1,1,2,2,2-pentafluoroetil)-estr-4,9-dien-3-ona o un derivado o un análogo de ella farmacéuticamente aceptable en una cantidad suficiente para la profilaxis o el tratamiento de una enfermedad hormona-dependiente en un mamífero.
7. Composición farmacéutica de acuerdo con la reivindicación 6, siendo la enfermedad cáncer de seno.
8. Composición farmacéutica de acuerdo con la reivindicación 6, siendo el mamífero un humano.
9. Composición farmacéutica de acuerdo con la reivindicación 6, la cual comprende además un antiestrógeno.

DOCUMENTO DE CESIÓN ASSIGNMENT DOCUMENT

Los suscritos,
(We, the undersigned)

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con domicilio en Berlin, Alemania
(domiciled in)

declaramos que somos los inventores de la invención que lleva el título
(declare that we are the inventors of the invention titled)

Use of Antiprogestins for Prophylaxis and Treatment of hormone-dependent Diseases

y que hemos cedido el derecho sobre esta invención en Colombia, junto con los privilegios
(and that we have assigned our rights over this invention in Colombia, together with its privileges)

y anexidades a favor de SCHERING AKTIENGESELLSCHAFT
(and attachments, to) Berlin, Rep. Fed. de Alemania

1) <i>Jens Hoffmann</i>	2) <i>Rosemarie Lichtner</i>
3) <i>Gerhard Siemester</i>	4) <i>Martin Schneider</i>
5) <i>Ulrike Fuhrmann</i>	

Urkundenrolle-Nr. R 165/2003

Ich habe das Mitwirkungsverbot nach § 3 Abs. 1 Nr. 7 BeurkG erläutert. Meine Frage, ob eine Vorbefassung im Sinne der Vorschrift vorliege, wurde verneint.

Die vor mir geleisteten Unterschriften

des Herrn Jens **H o f f m a n n**,
geboren am 9. Januar 1963,

der Frau Rosemarie **L i c h t n e r**,
geboren am 21. April 1949,

des Herrn Gerhard **S i e m e i s t e r**,
geboren am 24. März 1959,

des Herrn Martin **S c h n e i d e r**,
geboren am 23. November 1951,

der Frau Dr. Ulrike **F u h r m a n n**,
geboren am 12. Mai 1959,

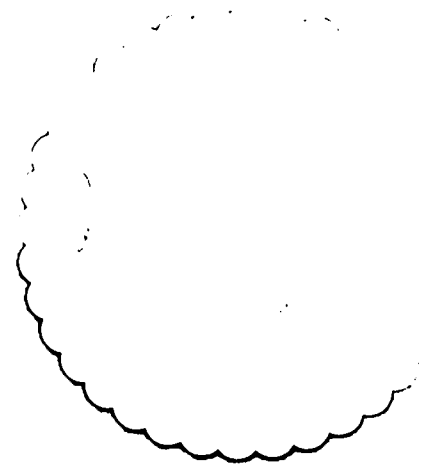
- von Person bekannt -

sämtlichst geschäftsansässig in 13353 Berlin, Müllerstraße 178,

beglaubige ich.

Berlin, 31. März 2003

Notar



Kostenberechnung gem. §§ 141, 154 KostO

Geschäftswert: 12.000,00 €

Beglaubigungsgebühr §§ 32, 45 I

Wegegebühr gem. § 58

Schreibauslagen §§ 136, 152

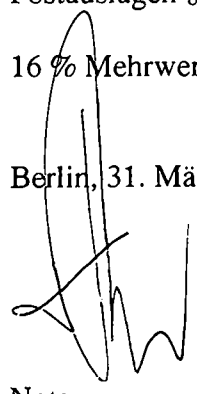
Postauslagen §§ 137, 152

16 % Mehrwertsteuer

15,00 €
15,00 €
1,00 €
1,44 €
32,44 €
5,19 €
37,63 €

Berlin, 31. März 2003

Notar



Apostille
(Convention de La Haye du 5 octobre 1961)

1. Land: Bundesrepublik Deutschland

Diese öffentliche Urkunde

2. ist unterschrieben von Dimitri R e m p e n

3. in seiner Eigenschaft als Notar

4. sie ist versehen mit dem Siegel
des Notars

Bestätigt

5. in Berlin

6. am 4. April 2003

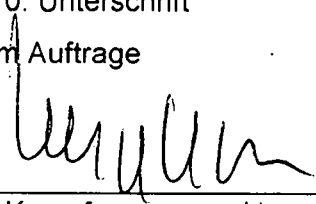
7. durch den Präsidenten des Landgerichts in Berlin

8. unter Nr. 9101 a E - F. 1010/2003

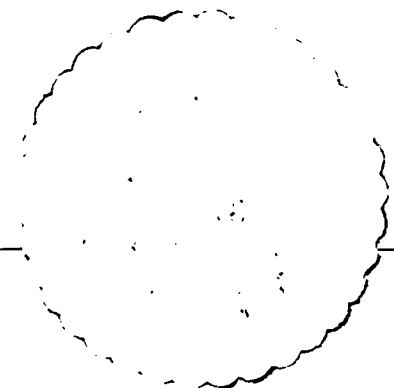
9. Siegel

10. Unterschrift

Im Auftrage


(Kupfernagel)

Vorsitzender Richter am Landgericht



Traducción Oficial del Alemán de la certificación la nota de gastos y la apostilla adjuntas al Documento de Cesión suscrito entre los inventores Jens Hoffmann, Rosemarie Lichtner, Gerd Siemeister, Martin Schneider y Ulrike Fuhrmann y la compañía Schering Aktiengesellschaft domiciliada en Berlín, Alemania.

Registro Notarial Número R 165/2003

Habiendo explicado la prohibición de participación conforme al Artículo 3 inciso 1 Numeral 1 de la Ley de Notarización, yo les pregunté a los participantes si existe algún impedimento en el sentido de dicha Ley. La respuesta fue negativa.

Autentico las firmas que aparecen anteriormente, las cuales fueron ejecutadas en mi presencia y pertenecen a

Señor Jens Hoffmann, nacido el 9 de Enero de 1963,

Señora Rosemarie Lichtner, nacida el 21 de Abril de 1949,

Señor Gerd Siemeister, nacido el 24 de Marzo de 1959,

Señor Martin Schneider, nacido el 23 de Noviembre de 1951,

Señora Ulrike Fuhrmann, nacida el 12 de Mayo de 1959,

todos ellos conocidos personalmente por el suscrito notario y domiciliados comercialmente en 13353 Berlín, Müllerstraße 178.

Berlín, 31 de Marzo del 2003

Dimitri Rempen, Notario en Berlín

(Firma y Sello Oficial)

----- (continúa en la 2ª página) -----

Nota de gastos según Artículos 141,154 Disposición Impuestos:

Valor del negocio: 12.000,00 EUROS

Impuesto Artículo 32, 45I Disp. Impuestos	15,00 EUROS
Impuesto Artículo 58 Disp. Impuestos	15,00 EUROS
Impuesto Artículos 136, 152 Disp. Impuestos	1,00 EUROS
Impuesto Artículos 137, 152 Disp. Impuestos	1,44 EUROS
I.V.A. 16%	5,19 EUROS
Total:	37,63 EUROS

Berlín, 31 de Marzo del 2003

Dimitri Rempen, Notario (firma)

APOSTILLA

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

1. País: República Federal de Alemania
Este documento público
2. Ha sido firmado por: Dimitri Rempen
3. En su calidad de: Notario
4. Y lleva el sello: Del mencionado Notario

Confirmado

5. En: Berlín
6. El día: 4 de Abril del 2003
7. Por: El Presidente del Tribunal Regional en Berlín
8. Bajo el No.: 9101 a E-F 1010/2003
9. Sello: EL PRESIDENTE DEL TRIBUNAL REGIONAL EN BERLIN
10. Firma: Por encargo: Kupfernagel,
Juez Presidente en el Tribunal Regional


ADOLF WATZKE
Traductor Oficial
Res. 2433 Minjusticia

SUPERINDUSTRIA Y COMERCIO

SISTEMA DE REGISTRO I

| Fecha 28/08/2003 |

|-----|

| MANTENIMIENTO DE PROTOCOLOS |

|Numero : 605 |

|Fecha : 15/01/1974 |

|Conferido: SCHERINGAKTIENGESSELLSCHAFT |

| |

|Pais : DE ALEMANIA |

|Ciudad : 355 BERGKAMEN |

|Represent: S Sustituir: S Desistir: S |

|No. Radicacion: 03-040568 Clase: Seev: Seac: |

|-----|

|scncia Codigo Ctr

|Nombre |

| 1 111 GOMEZ PRYOR FANNY LUCIA |

| 2 111 A PRYOR VARON HERNANDO |

| 3 126 CASTILLO PINEDA PEDRO |

| Encontrados (1/1) registro(s) |

|-----+

REQUISITOS NECESARIOS PARA PRESENTACION DE TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCION ✓		
MODELO DE UTILIDAD		
- Indicación de que se solicita la concesión de una patente.	()	()
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.	()	()
- Descripción de la invención.	()	()
- Dibujos de ser estos pertinentes.	()	()
- Comprobante de Pago de las tasas establecidas.	()	()
COMPLETA ()		
INCOMPLETA ()		
DISEÑO INDUSTRIAL ()		
- Indicación de que se solicita el registro de Diseño Industrial	()	()
- Datos de identificación del solicitante o de la persona que presenta la solicitud.	()	()
- Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	()	()
- Comprobante de pago de las tasas establecidas	()	()
COMPLETA ()		
INCOMPLETA ()		
ESQUEMA DE TRAZADO ()		
- Indicación de que solicita el registro de un Esquema de trazado.	()	()
- Datos de identificación del solicitante o de la persona que presenta La solicitud.	()	()
- Representación gráfica del esquema de trazado	()	()
- Comprobante de pago de las tasas establecidas.	()	()
COMPLETA ()		
INCOMPLETA ()		

Firma Responsable: ANDREA POSSE

Fecha: