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(54) Title: PHARMACEUTICAL PREPARATIONS AND METHODS FOR THEIR REGIONAL ADMINISTRATION

(57) Abstract

Formulations have been developed for regional delivery of drugs, for example, into a cavity such as the pelvic region, peritoneal region, or directly on organs of interest. Regional delivery increases comfort and bioavailability of the drug, resulting in rapid and relatively high blood levels in the regions to be treated in the substantial absence of side effects due to the high levels required for efficacy following systemic delivery. In the preferred embodiment, these formulations consist of drug micro or nanoparticles, which may be formed of drug alone or in combination with an excipient or polymeric carrier. The excipient or polymer may be used to manipulate release rates and to increase adhesion to the affected region. The drug formulation can be applied as a dried powder, a liquid suspension or dispersion, or as a topical ointment, creme, lotion, foam or suppository.

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PHARMACEUTICAL PREPARATIONS AND METHODS FOR THEIR REGIONAL ADMINISTRATION

Field of the Invention

The present invention relates to pharmaceutical preparations, and especially pharmaceutical formulations that can be introduced topically, locally, intrapelvically, intraperitoneally or directly on reproductive organs of interest in amounts effective to treat various conditions, particularly local diseases of the female reproductive system, such as pelvic, uterine, cervical and vaginal diseases which are present in this region of the body.

Background of the Invention

It has long been known that treatment of female reproductive diseases by traditional methods of oral or systemic administration is associated with drug bioavailability problems and concomitant side effect complications from unwanted absorption of drugs into the systemic circulation. For example, normal digestive tract action may break down orally administered active ingredients to decrease effective drug delivery dosages, or the pharmaceutical preparation may be changed by passage through the liver or by systemic circulation or may not achieve adequate levels in the area of interest. To counteract these undesirable actions, the dosage of the active ingredient needs to be increased, oftentimes leading to undesirable side effects.

Danazol, an isoxazolo derivative of 17α ethenyltestosterone (an androgen hormone), is commonly administered to women for treatment of endometriosis, range up to 800 mg daily. At high doses, adverse side effects are seen which may include weight gain, voice change, development of

facial and chest hair, loss of libido, acne, and central nervous system ("CNS") symptoms such as depression, anxiety, fatigue, nausea and diarrhea, as well as the inhibition of pregnancy while undergoing treatment. *See*, for example, Spooner, *Classification of Side Effects to Danazol Therapy*, Winthrop Laboratories, Surrey, England.

It is therefore highly desirable to provide new systems and methods for the administration of pharmaceuticals which would avoid such drawbacks. Mizutani, et al., in Fertility and Sterility 63, 1184-1189 (1995), describes administration of danazole vaginally by means of a 100 mg suppository, and compared the results with oral administration of a 400 mg dosage. No effect on the hypothalamic-pituitary-ovarian axis was noted, although high concentrations were present in the ovary, uterus and serum, with insignificant serum levels, following vaginal administration. Mizutani, et al., conducted their study following a report by Igarishi, Asia-Oceania J. Obstet. Gynaecol. 16(1), 1-12 (1990), that administration of danazole in a silicone vaginal ring reduced endometriotic tissue in the uterus and increased the incidence of pregnancy in treated women to a statistically significant degree. The immediate drawback to both therapies, however, is that the formulation and delivery platform such as vaginal rings and other devices are particularly unsatisfactory for women who already suffer from the cramps and pains associated with endometriosis. The dosages which were used were also quite high and extremely variable and may potentially have a negative and accumulative depot effect.

It is therefore an object of the present invention to provide formulations which are effective in treating disorders of the reproductive

organs which has high patient compliance and comfort.

It is a further object of the present invention to provide formulations and methods of administration which provide for extremely rapid uptake of drug in the affected region, with low systemic concentrations and few concordant side effects.

It is still another object of the present invention to provide greatly enhanced bioavailability of drug in formulations administered topically or locally, intrapelvically, intraperitoneally or directly on reproductive organs of interest as compared to the drugs administered in controlled release devices.

Summary of the Invention

Formulations have been developed for topical or local delivery of drugs intrapelvically, intraperitoneally or directly onto organs of interest, to produce a regional effect, with lower systemic drug levels than obtained when an effective dosage is systemically administered. In a preferred embodiment, drug is administered to a region such as the female reproductive system, provide for increased comfort, increased bioavailability, rapid and relatively high blood levels in the region to be treated without causing systemic levels of drug which might cause side effects. The preferred formulations consist of drug micro or nanoparticles, which may be formed of drug alone or in combination with an excipient or polymeric carrier. The excipient or polymer may be used to manipulate release rates and to increase adhesion of the drug to the affected region. The drug formulation can be applied as a dry powder, a liquid suspension or dispersion, a hydrogel

suspension or dispersion, sponges, or as a topical ointment, creme, lotion, foam or suppository.

Specific danazole formulations are described. Rat studies demonstrate rapid uptake of danazole into the tissues affected in endometriosis, with serum drug levels that are almost undetectable.

Detailed Description of the Invention

The compositions and methods for administration thereof provide for significantly diminished side effects with increased bioavailability and comfort, as compared to conventional drug administration techniques, and avoid the need for oral and parenteral administration, the use of complex and expensive biocompatible polymeric material, and insertion into the body and maintenance therein of potentially infectious foreign objects, such as intrauterine devices, vaginal rings, and suppositories.

I. Formulations.

The formulations are designed to provide maximum uptake in the affected tissues with rapid dissemination throughout the region to be treated, with little to no increase in systemic blood levels of the drug. The formulations can consist solely of drug, or drug combined with excipient or polymeric material.

A. Drugs

The term "drug" can refer to any pharmaceutically active substance capable of being administered in a particulate formulation, which achieves the desired effect. Drugs can be synthetic or natural organic compounds, proteins or peptides, oligonucleotides or nucleotides, or polysaccharides or sugars. Drugs may have any of a variety of activities, which may be inhibitory or stimulatory, such as antibiotic activity, antiviral

activity, antifungal activity, steroidal activity, cytotoxic or anti-proliferative activity, anti-inflammatory activity, analgesic or anesthetic activity, or be useful as contrast or other diagnostic agents. A description of classes of drugs and species within each class can be found in Martindale, *The Extra Pharmacopoeia*, 31st Ed., *The Pharmaceutical Press*, London (1996) and goodman and Gilman, *The Pharmacological Basis of Therapeutics*, (9th Ed., McGraw-Hill Publishing company (1996).

Examples of compounds with steroidal activity include progestins, estrogens, antiestrogens and antiprogestins.

In a preferred embodiment, the drug is danazole or gestrinone in a micro or nanoparticulate formulation. This can be achieved by milling of the drug or atomization of drug solution, for example, into a solvent extraction fluid, or other standard techniques. The danazole or gestrinone can be present as a complex with a cyclodextrin, for example, hydroxypropyl-β-cyclodextrin (HPB).

In another preferred embodiment, the drug is a polysaccharide, preferably a sulfated polysaccharide. Examples of suitable sulfated polysaccharides include carageenan, dextran sulfate, heparin, and fucoidin.

B. Excipients or Carriers

The drug substance may be "associated" in any physical form with a particulate material, for example, adsorbed or absorbed, adhered to or dispersed or suspended in such matter, which may take the form of discrete particles or microparticles in any medicinal preparation, and/or suspended or dissolved in a carrier such as an ointment, gel, paste, lotion, sponge, or spray.

Standard excipients include gelatin, casein, lecithin, gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glyceryl monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, polyethylene glycols, polyoxyethylene stearates, colloidol silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethycellulose phthalate, noncrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, polyvinylpyrrolidone, sugars and starches.

C. Polymeric Materials

In a preferred embodiment, the drug is present on or within micro or nanoparticulates formed of a polymeric material. Additional materials, such as diagnostic agents, including echogenic gases, radioactive materials - which may also in themselves be therapeutic, and magnetic materials for detection by MRI or PET, can optionally be included in the particles.

Various polymers can be used to increase adhesion to mucosal surfaces, to control release as a function of the diffusion rate of drugs out of the polymeric matrix and/or rate of degradation by hydrolysis or enzymatic degradation of the polymers and/or pH alteration, and to increase surface area of the drug relative to the size of the particle.

The polymers can be natural or synthetic, and can be biodegradable or non-biodegradable. High molecular weight drugs can be delivered partially by diffusion but mainly by degradation of the

polymeric system. For this reason, biodegradable polymers, bioerodible hydrogels, and protein delivery systems are particularly preferred when high molecular weight drugs are being delivered.

The polymers may be natural or synthetic polymers, although synthetic polymers are preferred due to the better characterization of degradation and release profiles. The polymer is selected based on the period over which release is desired, generally in the range of at least immediate release to release over a period of twelve months, although longer periods may be desirable. In some cases linear release may be most useful, although in others a pulse release or "bulk release" may provide more effective results. The polymer may be in the form of a hydrogel (typically absorbing up to about 90% by weight of water), and can optionally be crosslinked with multivalent ions or polymers.

Representative natural polymers include proteins such as zein, modified zein, casein, gelatin, gluten, serum albumin, and collagen, polysaccharides such as cellulose, dextrans, and polyhyaluronic acid.

Representative synthetic polymers include polyphosphazenes, poly(vinyl alcohols), polyamides, polycarbonates, polyacrylates, polyalkylenes, polyacrylamides, polyalkylene glycols, polyalkylene oxides, polyalkylene terephthalates, polyvinyl ethers, polyvinyl esters, polyvinyl halides, polyvinylpyrrolidone, polyglycolides, polysiloxanes, polyurethanes and copolymers thereof.

Examples of suitable polyacrylates include poly(methyl methacrylate), poly(ethyl methacrylate), poly(butyl methacrylate), poly(isobutyl methacrylate), poly(hexyl

methacrylate), poly(isodecyl methacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate) and poly(octadecyl acrylate).

Synthetically modified natural polymers include cellulose derivatives such as alkyl celluloses, hydroxyalkyl celluloses, cellulose ethers, cellulose esters, and nitrocelluloses. Examples of suitable cellulose derivatives include methyl cellulose, ethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, hydroxybutyl methyl cellulose, cellulose acetate, cellulose propionate, cellulose acetate butyrate, cellulose acetate phthalate, carboxymethyl cellulose, cellulose triacetate and cellulose sulfate sodium salt.

Each of the polymers described above can be obtained from commercial sources such as Sigma Chemical Co., St. Louis, MO., Polysciences, Warrenton, PA, Aldrich Chemical Co., Milwaukee, WI, Fluka, Ronkonkoma, NY, and BioRad, Richmond, CA. or can be synthesized from monomers obtained from these suppliers using standard techniques. The polymers described above can be separately characterized as biodegradable, non-biodegradable, and bioadhesive polymers, as discussed in more detail below.

1. Biodegradable polymers

Representative synthetic degradable polymers include polyhydroxy acids such as polylactides, polyglycolides and copolymers thereof, poly(ethylene terephthalate), poly(butic acid), poly(valeric acid), poly(lactide-co-caprolactone), polyanhydrides, polyorthoesters and blends and copolymers thereof.

Representative natural biodegradable polymers include polysaccharides such as alginate, dextran, cellulose, collagen, and chemical derivatives thereof (substitutions, additions of chemical groups, for example, alkyl, alkylene, hydroxylations, oxidations, and other modifications routinely made by those skilled in the art), and proteins such as albumin, zein and copolymers and blends thereof, alone or in combination with synthetic polymers. In general, these materials degrade either by enzymatic hydrolysis or exposure to water *in vivo*, by surface or bulk erosion.

2. Non-Biodegradable Polymers

Examples of non-biodegradable polymers include ethylene vinyl acetate, poly(meth)acrylic acid, polyamides, polyethylene, polypropylene, polystyrene, polyvinyl chloride, polyvinylphenol, and copolymers and mixtures thereof.

3. Bioadhesive polymers

Hydrophilic polymers and hydrogels tend to have bioadhesive properties. Hydrophilic polymers that contain carboxylic groups (e.g., poly[acrylic acid]) tend to exhibit the best bioadhesive properties. Polymers with the highest concentrations of carboxylic groups are preferred when bioadhesiveness on soft tissues is desired. Various cellulose derivatives, such as sodium alginate, carboxymethylcellulose, hydroxymethylcellulose and methylcellulose also have bioadhesive properties. Some of these bioadhesive materials are water-soluble, while others are hydrogels.

Rapidly bioerodible polymers such as poly(lactide-co-glycolide), polyanhydrides, and polyorthoesters, whose carboxylic groups are exposed on the external surface as their smooth surface erodes, can also be used for bioadhesive

drug delivery systems. In addition, polymers containing labile bonds, such as polyanhydrides and polyesters, are well known for their hydrolytic reactivity. Their hydrolytic degradation rates can generally be altered by simple changes in the polymer backbone. Upon degradation, these materials also expose carboxylic groups on their external surface, and accordingly, these can also be used for bioadhesive drug delivery systems.

D. Hydrogel Matrices

In another preferred embodiment, the drug is present as a dispersion of micro- or nanoparticles in a hydrogel matrix. The hydrogel matrix can be used to cause the particles to remain at a particular location over an extended period of time, particularly when the hydrogel is adhered to a tissue surface. The use of hydrogels to provide local delivery of drugs is described, for example, in U.S. Patent No. 5,410,016 to Hubbell et al.

The particles to be incorporated in the hydrogel matrix can be formed of drug alone, or can include the excipients and/or polymers described above. The drug can also be added as a dispersion or solution to the matrix. The drug can be released from the particles through dissolution of the particles, the hydrogel or both. Suitable hydrogels can be formed from synthetic polymers such as polyethylene glycol, polyethylene oxide, polyvinyl alcohol, polyvinyl pyrrolidone, polyacrylates, poly (ethylene terephthalate), poly(vinyl acetate), and copolymers and blends thereof, as well as natural polymers such as cellulose and alginate, as described above. Exemplary materials include SEPTRAFILM™ (modified sodium hyaluronate/carboxymethylcellulose, Genzyme Pharmaceuticals) and INTERCEED™ (oxidized

regenerated cellulose, Johnson & Johnson Medical, Inc.)

II. Methods of Administration

The formulations are preferably administered locally within the region to be treated, for example, vaginally for treatment of diseases of the ovaries and uterus. As used herein, "locally" can refer to topical application generally to the mucosal or endometrial surfaces of the vagina and/or uterus, or to a particular portion of the vagina or uterus. As used herein, "regionally" refers to reproductive organs and their surrounding environs, which include uterus, fallopian tube, peritoneal space, pelvic cul-de-sac, ovaries, perineum, abdominal; the rectovaginal region and corresponding regions in men, and urinogenital tract, including bladder, urinary tract, and rectum. As used herein, "systemically" refers to the circulatory system, and regions outside the spaces described above.

Vaginally administered pharmaceutical preparations as described herein are particularly effective in treating certain diseases of female reproductive systems, such as the administration of danazol for treatment of endometriosis, and in the treatment of other disorders such as urinary incontinence. It is desirable to administer the danazol formulations locally with dosages which are less than other modes of delivery, such as oral delivery. Transdermal doses are usually found to be one-quarter of the oral dose for similar efficacy. In this instance, it is possible to lower the dose even lower (the ring delivered between about 1 and 2 mg/day). Such dosage administration will ensure negligible or relatively low serum levels of danazol to avoid undesirable

side effects associated with oral dosing, such as hirsutism and other androgenic side effects.

The following non-limiting examples more fully demonstrate the present invention.

EXAMPLE 1: Preparation of Gel Products.

The drug substance, micronized danazol (carrying DMF-Drug Master File Certification) was manufactured by Cipla Pharmaceuticals and bought from Byron Chemical Company. UV absorption identified the drug substance as being identical to Danazol USP. Individual impurities were noted to be not more than 0.5%, and total impurities not more than 1.0%. Assay of dried basis was between 97% and 102% w/w on dried basis. More than 90% of the particles were less than 5 microns in diameter and the remaining particles were between 5 and 15 microns in diameter.

Micronized danazol was levigated in a commercial preparation of KY Jelly, which is made up of a polymer hydroxyethyl cellulose to 10 ml volume (based on weight using density of jelly of 2.16 g/ml) to deliver a dosage of 1 mg in 50 μl. Gels were smooth in consistency, uniformly white and flowable. Particle size measurements were conducted with a Coulter H4mD particle size analyzer and were noted to be as follows:

Danazol Powder:

Average of 6 measurements	3.2μg
Individual measurement and variation	3.2μg ± 9μg

1 mg gel:

Average of 5 measurements	3.0μg
Individual measurement and variation	3.4μg ± 1.5μg

EXAMPLE 2: Administration of Danazole microparticulate formulation to rats.

Mature female Sprague-Dawley rats were used for the experiment. 1 mg of the microparticulate

danazol was delivered in a volume of 50 μl to the vaginal vault and the animals sacrificed at the times noted below. The uterus and ovaries were separately homogenized and blood was drawn. All tissues and biological samples were processed. Danazol was extracted and assayed by HPLC methodology.

Danazol clinical assay:

Danazol was extracted from serum and tissue hexane/chloroform 80/20. For tissues, 1 ml aliquote of each homogenate was taken. The extracted danazol was reconstituted in a water/acetonitrile mobile phase and a Beckman Ultrasphere 5 micron, 4.6 mm X 15 cm reverse phase column (C-18 RP) was used for all the HPLC analyses. A danazol recovery study was conducted using danazol drug product. The recovery was determined by comparing the extracted signal with unextracted signal. A recovery of between 75 and 84% was obtained for the extraction method.

Study Results:

Tissue and serum levels are summarized below in Table 1:

Table 1: Tissue and Serum Levels of Danazole in Rats

RATE AND TIME	UTERUS—ng/g	OVARIES ng/g	SERUM ng/ml
2 hours	0.43	0.33	0.21
4 hours	0.57	not detected	not detected
6 hours	0.77	not detected	not detected

The results of this study demonstrate that the formulation used resulted in a preferential absorption of danazol into the uterus.

In the above examples, danazol concentrations of 1 mg/300 g rat were administered. In work by Mizutami, danazol concentrations of 100 mg/50 kg

women were administered. These concentrations are roughly equivalent. The data demonstrate that the suppository used by Mizutami resulted in uterine concentrations of danazol which were 10^5 times higher than the uterine concentrations of danazol provided by the microparticles in the above examples. Such high local concentrations could result in significant changes in the local delivery of the drug and effects on the reproductive organs, for instance, changes in hormone steroid responsiveness and depot effect.

Igarashi administered a vaginal ring contained in silicone. This type of drug delivery device releases drug in a constant manner, creating a continuous flow of drug and potentially to a depot effect. Igarashi discloses two examples in which danazol was administered via the vaginal ring. In both examples, the uterine concentration of danazol was 100 times higher than the uterine concentration in the above examples.

EXAMPLE 3: Protocol for Studies in Primate Models of Endometriosis.

Microparticle formulation allows for considerable decrease in delivered dose, increased bioavailability to the organs of interest with lower tissue concentrations.

Monkey Protocol:

The monkey study will demonstrate efficacy of the microparticle formulation in an animal model of endometriosis, while also evaluating systemic levels of locally delivered danazol. The simian model of endometriosis will be used to demonstrate efficacy and safety. The rationale for using monkeys is the finding that certain monkeys will naturally develop endometriosis which resembles, in crucial ways, the human disease. In addition, monkeys are a good model for studying the human

female reproductive system, both anatomically and physiologically for testing a vaginal product such as Danazol TVDT. This study will assist in identifying the dose needed to treat human endometriosis and furthermore, corroborate preliminary evidence that danazol can be delivered vaginally for treatment of endometriosis with reduced systemic levels. Microparticle danazol will be formulated in the presence of poly(vinylpyrrolidone). Three doses of Danazol TVDT will be studied in monkeys with endometriosis and compared to orally delivered danazol as described below. The study will be a nine week, parallel, randomized study comparing the effects of oral danazol given at 200 mg daily and three doses of Danazol TVDT: at 10 mg/day; (one-twentieth the oral dose), 25 mg/day (one-tenth the oral dose) and 50 mg/ day, (one quarter the oral dose). The results will demonstrate local delivery of microparticle danazol results in efficacy and low systemic levels.

We claim:

1. A micro or nanoparticulate drug formulation suitable for local or regional topical administration of an effective amount to provide relief from symptoms in a region in patients in need thereof.

2. The formulation of claim 1 wherein the region is the female reproductive organs.

3. The formulation of claim 2 wherein the patients have a disorder located in the reproductive organs.

4. The formulation of claim 1 wherein the formulation comprises drug particles.

5. The formulation of claim 3 wherein the drug is for treatment of endometriosis.

6. The formulation of claim 1 wherein the micro or nano particulates adhere to mucosal tissue.

7. The formulation of claim 1 where the micro or nano particulates comprise polymer altering rates of drug absorption in the region to be treated.

8. The formulation of claim 1 which can be administered vaginally, intraperitoneally, or directly on the reproductive organs of interest.

9. The formulation of claim 8 wherein the drug is danazol and wherein the formulation is suitable for vaginal administration in patients in need thereof and is in a dosage effective for treatment of endometriosis.

10. The formulation of claim 1 wherein the drug is an anticancer drug, cytotherapeutic or anti-proliferative drug in a dosage effective for treatment of cancer in the region of the patient where administered.

11. The formulation of claim 1 wherein the drug is an antiviral agent effective for treatment

of viral infections selected from genital herpes and genital papilloma viral infections.

12. The formulation of claim 1 wherein the drug is an antifungal agent effective for treatment of vaginal fungal infections.

13. The formulation of claim 1 wherein the drug is an antibacterial agent effective for treatment of vaginal and endometrial bacterial infections.

14. The formulation of claim 1 wherein the drug is a steroid or steroid-like product suitable for treatment of endocrine conditions.

15. The formulation of claim 14 wherein the drug is effective for treatment of menopause, infertility, contraception, dysfunctional uterine bleeding, dysmenorrhea, adenomyosis, or assisted reproductive technologies.

16. A method of treating a patient comprising the step of administering to the patient an effective amount of a micro or nanoparticulate drug formulation suitable for local or regional topical administration of an effective amount to provide relief from symptoms in a region in the patient in need thereof.

17. The method of claim 17 wherein the region is the female reproductive organs.

18. The method of claim 17 wherein the patients have a disorder located in the reproductive organs.

19. The method of claim 18 wherein the drug is for treatment of endometriosis and the patient has endometriosis.

20. The method of claim 17 which can be administered vaginally, intraperitoneally, or directly on the reproductive organs of interest.

21. The method of claim 16 wherein the drug is danazol and wherein the formulation is vaginally

administered in patients in need thereof in a dosage effective for treatment of endometriosis.

22. The method of claim 16 wherein the drug is an anticancer drug, cytotherapeutic or anti-proliferative drug in a dosage effective for treatment of cancer in the region of the patient where administered.

23. The method of claim 16 wherein the drug is an antiviral agent effective for treatment of viral infections selected from genital herpes and genital papilloma viral infections.

24. The method of claim 16 wherein the drug is an antifungal agent effective for treatment of vaginal fungal infections.

25. The method of claim 16 wherein the drug is an antibacterial agent effective for treatment of vaginal and endometrial bacterial infections.

26. The method of claim 16 wherein the drug is a steroid or steroid-like product suitable for treatment of endocrine conditions.

27. The method of claim 26 wherein the drug is effective for treatment of menopause, infertility, contraception, dysfunctional uterine bleeding, dysmenorrhea, adenomyosis, or assisted reproductive technologies.

28. A method for treating endometriosis comprising administering to the mucosal membranes of the female reproductive tract danazole in a form promoting quick uptake into the blood stream.

29. The method of claim 28 wherein the danazole is in a form selected from the group consisting of foams, tablets, and creams.

30. The method of claim 28 wherein the danazole is in a form suitable for application to the uterus.

31. A composition for treating endometriosis comprising danazole in a form promoting quick

uptake into the blood stream when applied to the mucosal membranes of the female reproductive tract.

32. The composition of claim 31 wherein the danazole is in a form selected from the group consisting of foams, tablets, and creams.

33. The composition of claim 32 wherein the danazole is in a form suitable for application to the uterus.

INTERNATIONAL SEARCH REPORT

Inter. ...nal Application No
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A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/06

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 921 636 A (ZAFFARONI ALEJANDRO) 25 November 1975 see column 6, line 38-60 see column 7, line 32 - column 8, line 10 see column 11, line 11 see column 11, line 15-17 see column 11, line 29-30 see examples 3,4 see claim 4 --- -/--	1-4,6-8, 13-20, 22,25-27

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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INTERNATIONAL SEARCH REPORT

Interr nal Application No
PCT/US 98/00916

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 566 135 A (TAKEDA CHEMICAL INDUSTRIES LTD) 20 October 1993 see page 3, line 20-31 see page 4, line 8-12 see page 8, line 15-40 see page 9, line 28 see claims 2,3	1-4,6-8, 10,11, 13-18, 20,22, 23,25-27

X	WO 96 37232 A (UNIV SANTIAGO COMPOSTELA ;ALONSO FERNANDEZ MARIA JOSE (ES); CALVO) 28 November 1996 see abstract see page 1, line 11-13 see page 2, line 3-5 see page 5, line 14-18 see page 6, line 5-8 see claim 13	1-4,6,8, 16-18

X	WO 95 07071 A (EDKO TRADING REPRESENTATION ;EMBIL KORAL (TR); MORTON OSWALD (GB)) 16 March 1995 see abstract see page 1, line 6-18 see page 5, line 31 - page 6, line 10 see page 9, line 11-20 see example 4 see claims 1,2,5,6,8	1-4,6-8, 12,13, 16-18, 20,24,25

X	US 5 510 118 A (BOSCH H WILLIAM ET AL) 23 April 1996	1,5,16, 19
Y	see column 3, line 65 - column 4, line 23 see column 5, line 30-31 see column 8, line 41-48 see table 1 see claim 6	9,21

X	EP 0 501 056 A (IGARASHI MASAO) 2 September 1992	28-33
Y	see abstract see page 3, column 3, line 1-6 see page 3, column 4, line 13-16 see page 3, column 4, line 31-39 see page 3, column 4, line 55 - page 4, column 5, line 7 see example see claims 1,2,15	9,21

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PCT/US 98/00916

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 997 653 A (IGARASHI MASAO) 5 March 1991 see abstract see column 1, line 8-13 see column 2, line 37-49 see column 3, line 63 see examples 3,4 see claims -----	28,30, 31,33

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INTERNATIONAL SEARCH REPORT

International application No.
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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

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

1. [X] Claims Nos.: 16-30
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 16-30 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. ›nal Application No
PCT/US 98/00916

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