



Office de la Propriété
Intellectuelle
du Canada

Un organisme
d'Industrie Canada

Canadian
Intellectual Property
Office

An agency of
Industry Canada

CA 2057714 C 2002/10/01

(11)(21) **2 057 714**

(12) **BREVET CANADIEN
CANADIAN PATENT**

(13) **C**

(22) Date de dépôt/Filing Date: 1991/12/16

(41) Mise à la disp. pub./Open to Public Insp.: 1992/06/18

(45) Date de délivrance/Issue Date: 2002/10/01

(30) Priorité/Priority: 1990/12/17 (90203371.1) EP

(51) Cl.Int.⁵/Int.Cl.⁵ A61K 31/565

(72) Inventeurs/Inventors:

Bergink, Engelbert Willem, NL;
Bennink, Herman Jan Tijmen Coelingh, NL

(73) Propriétaire/Owner:

Akzo N.V., NL

(74) Agent: FETHERSTONHAUGH & CO.

(54) Titre : CONTRACEPTIF A ACTION UNIQUEMENT PROGESTATIVE

(54) Title: PROGESTAGEN-ONLY CONTRACEPTIVE

(57) Abrégé/Abstract:

Disclosed is an oral contraceptive regimen containing daily dosage units each containing from 70 to 80 micrograms of desogestrel, 3-ketodesogestrel or mixtures thereof. It has been found that by making a selection of desogestrel or 3-ketodesogestrel at the described dosages in an oral contraceptive regimen administered over the entire menstrual cycle (e.g. 28 days), effective ovulation inhibition is achieved and intermenstrual bleeding is avoided, while acceptable cycle control is retained. Moreover, the regimen also prevents the formation of persistent ovarian cysts.



Abstract of The Disclosure

Disclosed is an oral contraceptive regimen containing daily dosage units each containing from 70 to 80 micrograms of desogestrel, 3-ketodesogestrel or mixtures thereof. It has been found that by making a selection of desogestrel or 3-ketodesogestrel at the described dosages in an oral contraceptive regimen administered over the entire menstrual cycle (e.g. 28 days), effective ovulation inhibition is achieved and intermenstrual bleeding is avoided, while acceptable cycle control is retained. Moreover, the regimen also prevents the formation of persistent ovarian cysts.

23804-336

1

PROGESTOGEN-ONLY CONTRACEPTIVE

Technical Field. The invention relates generally to contraceptive preparations, and more specifically to a contraceptive regimen involving only the administration of desogestrel, 3-ketodesogestrel or mixtures thereof.

Background Art. It has been known for some time that contraception can be achieved by the oral administration of sufficient quantities of a progestogen to a female of child-bearing age.

For example in French Patent Application No. 2,223,018 to Ortho Pharmaceutical, a progestogen is administered from at least the fifth day to the twenty-fifth day of the menstrual cycle, the dosage of the progestogen being greater during the last seven days of administration than it is in the first seven days.

U.S. Patent No. 4,018,919 to Eli Lilly & Co. describes a sequential oral contraceptive method using two different types of progestational agents. These different types of progestational agents are a Type A progestin (e.g. norethindrone) and Type B progestin (e.g. chlormadione acetate).

Another contraceptive regimen using these two types of progestational agents is described in Belgian Patent 773,064 to Ciba Geigy AG.

U.S. Patent 4,171,358 to Eli Lilly & Co. describes another contraceptive method in which a progestin (e.g. chlormadione acetate) is administered on days 6 to 16 of the menstrual cycle, followed by a period in which no hormone is administered.

German Patent 1,950,857 to Merck Patent GmbH describes a progestogen-only contraceptive pack containing 28 dosage units, 14 to 18 of which are "blanks", containing no contraceptive steroid. Disclosed progestogens include chlormadione acetate, megestrol acetate, melengestrol acetate and medroxyprogesterone acetate. A similar reg-

23804-336

2

imen is disclosed in German Patent 1,965,881, also to Merck Patent GmbH.

U.S. Patent No. 3,822,355 to Biological Concepts Inc. describes a method of controlling the ovulatory cycle in women involving administering placebo tablets daily for 12 to 16 days; followed administering daily tablets containing 2 to 20 mg progestogen (e.g. norethindrone) for four days; finally followed by administering tablets containing 10 to 40 % of the previous progestogen dosage for the remainder of the cycle.

"Progestogen-only pills" are a preferred method of contraception for breast-feeding mothers, older women, women for whom estrogen is contraindicated, women who are hypertensive, and women who develop migraine headaches when taking a combined pill (i.e. one containing an estrogen and progestogen component). See, e.g. "Contraception for women over the age of 35", IPPF Medical Bulletin, 22: 3-4 (1988) and Howie, PW "The progestogen-only pill", Brit. J. Obstet. Gynaecol., 92: 1001-2 (1985).

While different progestogen-only regimens have been described, they are still associated with incomplete ovulation inhibition, and relatively high failure rates. Vessey et al "Progestogen-only oral contraception. Findings in a large prospective study with special reference to effectiveness", Brit. J. Family Planning, 292: 526-30 (1986). It has been suggested to increase the daily dosage of progestogen in order to induce complete ovulation inhibition, however such an increase in dosage also increases the frequency of intermenstrual bleeding (i.e. "spotting"), which is clearly not desired. E. Diczfalusy et al, Progestogens in Therapy, p. 150 (Raven Press, NY 1983).

Moreover, a high prevalence of functional ovarian cysts have been reported with progestogen only contraceptive regimens, which resolve after discontinuation of the progestogen-only contraceptive. Fotherby, K. "The Progestogen-pill", in: Filshie et al eds. Contracep-

23804-336

3

tion: Science and Practice, pp. 94-108 (1989), and Howie,
supra.

A need exists for a progestogen-only contraceptive regimen which more effectively inhibits ovulation, while
5 still not increasing the frequency of intermenstrual bleeding, or leading to persistent functional ovarian cysts.

Disclosure of the Invention

Surprisingly it has been found that by selecting desogestrel or 3-ketodesogestrel as the progestogen at
10 certain specified dosages for use in an oral contraceptive regimen administered over an entire menstrual cycle (e.g. 28 days), complete ovulation inhibition is achieved, while retaining acceptable cycle control. Moreover, this regimen also seems to prevent the formation of ovarian cysts, and
15 decreases the amount of spotting.

The invention thus includes a drug delivery system containing daily oral dosage units, each unit containing from 70 to 80 micrograms of desogestrel, 3-ketodesogestrel, or mixtures thereof.

20 In another aspect the present invention includes a contraceptive kit comprising sequential daily dosage units for oral administration each containing as the sole contraceptively effective ingredient from 70 to 80 micrograms of desogestrel, 3-ketodesogestrel, or mixtures
25 thereof.

The invention also includes a pharmaceutical product (i.e. the dosage units or the package containing the dosage units), a method of using the product, and a process of manufacturing the pharmaceutical product.

23804-336

3a

In yet another aspect the invention includes a process of manufacturing a drug delivery system comprising: mixing predetermined quantities of a progestogen selected from the group consisting of desogestrel, 3-ketodesogestrel, and mixtures thereof, with predetermined quantities of excipients and converting the mixture into dosage units each containing 70 to 80 μ g of desogestrel, 3-ketodesogestrel, or mixtures thereof, and packaging a plurality of said dosage units into a kit.

10 The invention also includes a method of providing contraception for a pre-menopausal woman involving orally administering to the woman, on a daily basis, 70 to 80 micrograms of desogestrel, 3-ketodesogestrel, or mixtures thereof.

15 Best Mode of the Invention

Progestogens for use with the invention are 3-ketodesogestrel ("etonogestrel") and desogestrel. Desogestrel has the chemical name 13-ethyl-11-methylene-18,19-dinor-17 α -pregn-4-en-20-yn-17-ol. Desogestrel is

believed to be metabolized in the body into 3-ketodesogestrel. In the dosage units, 75 µg of desogestrel or 3-ketodesogestrel are preferably used. Both compounds are available from Organon International, bv of Oss, The Netherlands.

The progestogen ("contraceptive steroid"), is incorporated into dosage units for oral administration. The term "dosage unit" generally refers to physically discrete units suitable as unitary dosages for humans, each containing a predetermined quantity of active material calculated to produce the desired effect.

Methods and compositions for making such dosage units are well-known to those skilled in the art. For example, conventional techniques for making tablets and pills, containing active ingredients, are described in the standard reference, Chase et al., Remington's Pharmaceutical Sciences, (16th ed., Mack Publishing Co., Easton. PA, U.S.A., 1980) ("Remington's"), at pages 1553 through 1584. Conventional techniques for making powders, and their composition are described at pages 1535 through 1552 of the reference. Conventional techniques for coating pharmaceutical dosage forms are described at pages 1585 to 1593 of Remington's.

For making dosage units, e.g. tablets, the use of conventional additives, e.g. fillers, colorants, polymeric binders and the like is contemplated. In general any pharmaceutically acceptable additive which does not interfere with the function of the active compounds can be used in the one or more of the compositions.

Suitable carriers with which the compositions can be administered include lactose, starch, cellulose derivatives and the like used in suitable amounts. Lactose is a preferred carrier. Mixtures of carriers can also be used.

A process of manufacturing the combination and contraceptive kit of the invention comprises mixing predetermined quantities of desogestrel, 3-ketodesogestrel, or mixtures thereof with predetermined quantities of excipients and converting the mixture into dosage units

containing 70 to 80 μ g of desogestrel or 3-ketodesogestrel.

Converting the mixture into dosage units generally involves molding the mixture into a tablet, filling a capsule with a dried mixture, or filling a capsule with a wet mixture.

A preferred process of manufacturing the pharmaceutical product according to the invention involves incorporating the desired dosages of contraceptive steroid (i.e. desogestrel, 3-ketodesogestrel, or mixtures thereof) into tablets by techniques such as wet granulation tableting techniques. The package containing the dosage units will contain between 7 and 180, preferably 28, dosage units.

A preferred method of contraception using the invention comprises administering, orally, to a female of child-bearing age, 70 to 80 μ g of desogestrel, 3-ketodesogestrel, or mixtures thereof daily. After the completion of one cycle of the regimen, the regimen may be repeated for as long as contraception is desired.

Desogestrel and 3-ketodesogestrel are 70 to 80 % bioavailable after oral administration in comparison with non-enteral forms of administration (e.g. via an implant).

The invention is further explained by the following illustrative EXAMPLES.

EXAMPLE I

The following coated tablets intended for once daily administration were made:

Composition (per tablet):

<u>Compound</u>	<u>Amount (mg/tablet)</u>
desogestrel	0.075
corn starch	6.500
povidone	1.950
stearic acid	0.650
colloidal silicone dioxide	0.650
dl- α -tocopherol	0.080
lactose	qsad 65.000

Coating layer: (filmcoat-dry)

<u>Compound</u>	<u>Amount (mg/tablet)</u>
hydroxypropylmethylcellulose	0.75
polyethylene glycol 400	0.15
titanium dioxide	0.1125
talc	0.1875

The tablets were packed in push-through packs. The push through packs are placed in folding cartons, which are additionally sealed in aluminum sachets.

EXAMPLE II

The following tablets intended for once daily administration are made:
Compositions of tablets:

<u>Compound</u>	<u>Amount (mg/tablet)</u>
3-ketodesogestrel	0.075
corn starch	6.500
povidone	1.950
stearic acid	0.650
colloidal silicone dioxide	0.650
dl- α -tocopherol	0.080
lactose	qsad 65.000

Coating layer:

<u>Compound</u>	<u>Amount (mg/tablet)</u>
hydroxypropylmethylcellulose	0.75
polyethylene glycol 400	0.15
titanium dioxide	0.1125
talc	0.1875

EXAMPLE III

The tablets of EXAMPLE I, along with similar tablets containing 0.030 and 0.050 mg of desogestrel were tested in 44 healthy female volunteers in a non-public, double-blind randomized study. Ovulation was completely inhibited with the tablets of EXAMPLE I (i.e. those containing 0.075 mg desogestrel), whereas incomplete inhibition of ovulation occurred at the other lower doses. Furthermore, the use of the tablets of EXAMPLE I also had the lowest percentage of bleeding and spotting days (mean of 22%) in comparison to 0.030 mg desogestrel (mean of 32%) and 0.050 mg (mean of 33%).

Amenorrhea occurred only once in the group administered the tablets of EXAMPLE I. No luteinized follicles were observed with the group administered the tablets of EXAMPLE I, while the group administered 0.030 mg daily had three cycles, and the group administered 0.050 mg daily had one cycle of luteinized follicles. Non-luteinized small follicular cysts (15-40 mm diameter) were observed in all dose groups during 50 to 75 % of the cycles investigated. Persistent cysts occurred in the 0.050 mg group (10 out of 32 cycles). Follicles regressed spontaneously in women administered 0.075 mg desogestrel daily, and persistent cyst formation was not observed in this group.

Reference herein to specific embodiments or examples should not be interpreted as limitations to the scope of the invention, which is defined by the appended claims.

23804-336

8

CLAIMS:

1. A contraceptive kit comprising sequential daily dosage units for oral administration each containing as the sole contraceptively effective ingredient from 70 to 80
5 micrograms of desogestrel, 3-ketodesogestrel, or mixtures thereof.
2. The contraceptive kit of claim 1 wherein said kit contains 21 to 35 of said daily sequential dosage units.
3. The contraceptive kit of claim 2 wherein 3-
10 ketodesogestrel is present as the sole contraceptively effective ingredient in a quantity of 75 micrograms per dosage unit.
4. The contraceptive kit of claim 2 wherein desogestrel is present as the sole contraceptively effective
15 ingredient in a quantity of 75 micrograms per dosage unit.
5. The use of an oral daily dosage unit consisting essentially of 70 to 80 micrograms of a progestogen selected from the group of progestogens consisting of desogestrel, 3-ketodesogestrel, or mixtures thereof, in the preparation of
20 a drug delivery system, said drug delivery system characterized by consisting of daily dosage units containing only the said progestogen as sole therapeutically effective ingredient.
6. A method of providing contraception for a pre-
25 menopausal woman consisting essentially of: orally administering to a pre-menopausal woman, on a daily basis for as long as contraception is desired, from 70 to 80 micrograms of a steroid selected from the group consisting of 3-ketodesogestrel, desogestrel, and mixtures thereof.

7. A drug delivery system comprising a package containing
26 to 30 daily sequential dosage units consisting
essentially of from 70 to 80 micrograms of a compound
selected from the group consisting of desogestrel, 3-
ketodesogestrel, and mixtures thereof.
8. A contraceptive kit of the type containing progestogen-
only daily dosage units, wherein the improvement
comprises using from 70 to 80 micrograms of 3-
ketodesogestrel, desogestrel, or mixtures thereof as
the progestogen in said daily dosage units.
9. A process of manufacturing a drug delivery system
comprising:
mixing predetermined quantities of a progestogen selected
from the group consisting of desogestrel, 3-
ketodesogestrel, and mixtures thereof, with
predetermined quantities of excipients and converting
the mixture into dosage units each containing 70 to 80
 μ g of desogestrel, 3-ketodesogestrel, or mixtures
thereof, and
packaging a plurality of said dosage units into a kit.
10. The process of claim 9 wherein said mixture is
converted into dosage units selected from the group
consisting of capsules and tablets.

Fetherstonhaugh & Co.,
Ottawa, Canada
Patent Agents