

PATENT SPECIFICATION

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(54) PHARMACEUTICAL COMPOSITIONS

(71) I, HERCHEL SMITH, of 500 Chestnut Lane, Wayne, Pennsylvania, United States of America of British nationality, do hereby declare the invention for which I pray that a patent may be granted to me and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a contraceptive composition and to a process for making it.

The conventional oral contraceptive tablet comprises two pharmaceutically active ingredients. One of these is an oestrogen and has the effect of inhibiting ovulation in a woman to whom it is administered. The other is a progestogen which functions to neutralise unpleasant side effects of the oestrogen and to regulate the menstrual cycle. In these conventional oral contraceptive tablets the amount of progestogen is normally 1 mg. or more and not below 0.5 mg.

U.K. Specification 1,041,280 discloses the progestational agent norgestrel (13 - ethyl - 17 α - ethynyl - 17 β hydroxygon - 4 - en - 3 - one) and recommends its use in pharmaceutical compositions in amounts from 1 mg. to 25 mg.

It has now been found that contraceptive compositions containing considerably smaller amounts of such a progestational agent show an anti-fertility effect which is distinguishable from that produced by the oestrogen of a conventional formulation, since ovulation still occurs during treatment with such low doses. It is believed that this effect is linked with its anti-oestrogenic activity. It is thus possible to produce a contraceptive composition which contains a non-oestrogenic antifertility agent (usually a progestogen) as the only active ingredient in a very small dose form.

The invention provides a contraceptive composition comprising 13 - ethyl - 17 α - ethynyl - 17 β - hydroxygon - 4 - en - 3 - one as anti-fertility agent in association with a pharmaceutically acceptable carrier:

- (a) in an amount in the range from 15 to 150 micrograms formulated for daily administration such that having regard for

the releasing properties of the composition in use, substantially all is released in one day or

- (b) the contraceptive composition is formulated as a delayed release composition for administration less frequently than daily with the anti-fertility agent present in an amount in the range from 15 to 150 micrograms multiplied by the number of days over which it is to be released.

The invention also provides a process for the preparation of a contraceptive composition as defined above in which 13 - ethyl - 17 α - ethynyl - 17 β - hydroxygon - 4 - en - 3 - one is brought into association with a pharmaceutically acceptable carrier.

The amount of anti-fertility agent used depends upon its anti-oestrogenic activity and thus depends upon whether it is used as the *d*-enantiomer or the racemate since the former is twice as active as the latter. It will also depend on the weight and metabolic constitution of the patient. Thus for most women the racemate is preferably used in an amount in the range from 50 to 100 micrograms (daily) while the *d*-enantiomer is used in the range 25 to 50 micrograms.

The contraceptive composition is suitably in the form of a tablet or capsule for oral daily administration. Normally tablets are taken each day and are not discontinued during menstruation.

The composition can also be injected, preferably intramuscularly, or can be in the form of a delayed release composition, such as an implant that can be located intermuscularly or subcutaneously; in this latter case the composition is designed to release the required amount of anti-fertility agent each day. This can be done, for example, by combining the agent with a plastic base or with a modified carboxymethylcellulose, that is modified to render it less water soluble such as by using a lower degree of substitution or higher degree of polymerisation or by blocking some of the carboxyl groups e.g. by esterification.

The anti-fertility agent is compounded with conventional pharmaceutical ingredients to give

the contraceptive composition which can be formulated in liquid or solid forms, for instance as capsules, tablets, suppositories, powders, dispersible granules, and cachets by combining them with conventional carriers. Such conventional carriers include magnesium carbonate or stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, low melting wax and cocoa butter. Diluents, flavouring agents, solubilisers, lubricants, suspending agents, binders or tablet-disintegrating agents can be employed. The active steroid can be formulated with an encapsulating material with or without other carriers.

Liquid preparations such as solutions, suspensions or emulsions can also be used. Such preparations include dispersion in a pharmaceutically acceptable carrier such as arachis oil or sterile water preferably containing a non-ionic surface active agent such as fatty acid esters or polyhydroxy compounds, e.g. sorbitan, (for instance polyethylene oxide acid esters such as Tween 80 (Registered Trade Mark)), aqueous starch in sodium carboxymethyl cellulose solution, aqueous propylene glycol or polyethylene glycol. Thus a water-propylene glycol solution can be used for par-

enteral injection and aqueous suspensions suitable for oral use can be made by utilising natural or synthetic gums, resins, methyl cellulose or other well-known suspending agents.

The compounds can be in unit dose form. The unit dose form can be a packaged composition, e.g. packeted powders, vials or ampoules, or for example, in the form of capsules, cachets or tablets or any number of these in packaged form.

In the examples below the steroid is used as the *d* - 13 β - compound or the *dl* - 13 β - compound and is so designated using the Horeau Reichstein Convention approved by Fieser and Fieser, Steroids (1959) at page 336 in which the enantiomer of 13 β - configuration is considered as the *d*-13 β - form and its antipode the enantiomer of 13 α (absolute) configuration is designated the *l*-13 β -form so that the racemate is the *dl* - 13 β - compound.

For simplicity in naming the compounds in the specification (apart from the examples in which the compounds are named using the Horeau Reichstein Convention) the nomenclature is based on the hydrocarbon gonane and this implies a 13 β -substituent.

A tablet for use as an oral contraceptive agent consists of the following ingredients:

<i>dl</i> -13 β -ethyl-17 α -ethynyl-17 β -hydroxygon-4-en-3-one	50 micrograms
Carboxymethyl cellulose (viscosity 400 cps)	15 mg.
Lactose powder	25 mg.
Redried corn starch	25 mg.
Magnesium stearate powder	4 mg.
Calcium silicate powder	q.s.
	200 mg.

The tablet is prepared by dissolving the steroid in benzene, mixing the solution with the right proportion of starch, drying the mix in a current of air, adding the remaining ingredients in the correct proportions, mixing them and compressing the composition obtained into slugs, and finally regranulating and compressing into tablets such that each contains 50 micrograms of steroid.

Alternatively the tablet is prepared by dissolving the steroid in benzene, mixing the solution with the lactose powder and drying the

mix in a current of air, then adding the carboxymethyl cellulose, calcium silicate and half the starch. With the powder thus obtained is mixed starch paste prepared from the remainder of the starch, the mixture is wet-granulated, the granules dried, the stearate added and the composition compressed into tablets such that each contains 50 micrograms of steroid.

A capsule for use as an oral contraceptive contains, in encapsulating gelatine the following ingredients:

<i>dl</i> -13 β -ethyl-17 α -ethynyl-17 β -hydroxygon-4-en-3-one	50 micrograms
Finely divided silica lubricant	5 mg.
Magnesium stearate powder	5 mg.
Powdered corn starch	113 mg.
Lactose powder	q.s.
	245 mg.

Microdose formulations for contraceptive use consists of the following ingredients:

	mg.			
<i>d</i> -13 β -ethyl-17 α -ethynyl-17 β -hydroxygon-4-en-3-one	0.015	0.025	0.050	0.075
Microcrystalline cellulose, N.F.	20.000	20.000	20.000	20.000
Amberlite IRP-88 (Registered Trade Mark) (Rohm and Haas)	1.000	1.000	1.000	1.000
Magnesium stearate, U.S.P.	0.220	0.220	0.220	0.220
Lactose, U.S.P. q.s. ad	100.00	100.00	100.00	100.000

Representative clinical histories to illustrate the use of 13 - ethyl - 17 α - ethynyl - 17 β - hydroxygon - 4 - en - 3 - one follow:

5 L.P., age 27 years; Gravida 3 para 2 abortions 1, coital frequency 3 times per week, regular menstrual cycles of 28 days, average duration of flow 5 days with average amount of flow. Occasional menstrual discomfort to slight degree. The patient received *dl* - 13 β - ethyl - 17 α - ethynyl - 17 β - hydroxygon - 4 - en - 3 - one, 0.075 mg. (75 micrograms) daily as one tablet from cycle day one of the menstrual period on a continuous daily basis without interruption. Menstrual cycles were 27 and 25 days in length, amount of flow was average or heavy, length of flow 6 and 4 days. 10 The only side effect reported was dysmenorrhea in second cycle. Efficacy: No pregnancy. Cycle control maintained. Minimal side effects. 15 The only side effect reported was dysmenorrhea in second cycle. Efficacy: No pregnancy. Cycle control maintained. Minimal side effects. 20

S.C., age 23 years; Gravida 0 para 0 abortions 0, coital frequency 3 times per week. 25 Menstrual cycles regular, average 29 days, average duration of flow 5 days. Amount of flow average, no menstrual discomfort. Patient received *dl* - 13 β - ethyl - 17 α - ethynyl - 17 β - hydroxygon - 4 - en - 3 - one, 0.050 mg. (50 micrograms) daily as one tablet on a continuous basis without interruption. Length of cycle 25 days, duration of flow 5 days, amount of flow average, no side effects. Efficacy: Patient did not become pregnant. Cycle control comparable with pre-treatment. 35

D.N., age 24 years; Gravida 4 para 4 abortions 0, coital frequency 4 times per week. Menstrual cycles regular, average 28 days, average duration of flow 4 days, amount of flow variable, menstrual discomfort occasional and moderate. Mode of administration: one tablet daily of *dl* - 13 β - ethyl - 17 α - ethynyl - 17 β - hydroxygon - 4 - en - 3 - one, 0.075 mg. (75 micrograms) on continuous basis. No pregnancy. 40 45

While the above completely relates to the use of the contraceptive composition in women, the same principle can be applied to animals; the amounts of anti-fertility agent required each day will almost certainly be different from that found suitable for a woman. 50

WHAT I CLAIM IS:—

1. A contraceptive composition comprising 13 - ethyl - 17 α - ethynyl - 17 β - hydroxygon - 4 - en - 3 - one as anti-fertility agent in association with a pharmaceutically acceptable carrier: 55

(a) in an amount in the range from 15 to 150 micrograms formulated for daily administration such that having regard for the releasing properties of the composition in use, substantially all is released in one day or 60

(b) the contraceptive composition is formulated as a delayed release composition for administration less frequent- 65



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(b) the contraceptive composition is formulated as a delayed release composition for administration less frequent-

- ly than daily with the anti-fertility agent present in an amount in the range from 15 to 150 micrograms multiplied by the number of days over which it is to be released.
- 5 2. A compression for daily administration according to Claim 1 which the anti-fertility agent is the racemate and the amount range is from 50 to 100 micrograms.
- 10 3. A composition for daily administration according to Claim 1 in which the anti-fertility agent is the *d*-enantiomer and the amount range is from 25 to 50 micrograms.
- 15 4. A composition according to any one of the Claims 1 to 3, formulated as a tablet or capsule for oral daily administration.
5. A composition according to any one of Claims 1 to 3 comprising the anti-fertility agent in association with a delayed release composition such as a plastic or a modified carboxymethyl cellulose.
- 20 6. A composition according to Claim 5 formulated as an implant.
7. A contraceptive composition according to claim 1 substantially as described herein and shown with reference to the examples.
- 25 8. A process for the preparation of a contraceptive composition according to Claim 1 in which 13 - ethyl - 17 α - ethynyl - 17 β - hydroxygon - 4 - en - 3 - one is brought into association with a pharmaceutically acceptable carrier.
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J. L. BETON,
Chartered Patent Agent,
John Wyeth & Brother Limited,
Huntercombe Lane South,
Taplow, Maidenhead, Berkshire.

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