Solid peroral contraceptive drug

Description

Field of the invention

The invention relates to a solid oral pharmaceutical form for contraception which comprises 17α-cyanomethyl-17-β-hydroxyestra-4,9-dien-3-one (dienogest) equal to or less than 2.0 mg and 17α-ethinylestradiol (ethinylestradiol) less than 0.030 mg, and where the dienogest is released proportionately in two phases and one of the phases is released with a time delay relative to the other phase. The pharmaceutical form additionally comprises a total ethinylestradiol content intended for non-slow (rapid) release.

General prior art

Oral contraceptive compositions consisting of a progestogen component and of an estrogen component were marketed for the first time in the early 1960s. Three essential properties characterize the profile of the "contraceptive pill": contraceptive reliability, a very good cycle control and a minimum of side effects.
Since the introduction of hormonal contraceptives, research has been directed at the possibility of producing pharmaceutical forms which, while the contraceptive reliability and cycle control remain good, reduces unwanted side effects such as, for example, arterial and venous thromboses and influencing of carbohydrate and lipid metabolism - caused by a higher content of progestogen and estrogen than needed for contraception. WO 98/004269 disclose inter alia the oral administration of a combination of 250 µg - 4 mg of dienogest and 10 µg - 20 µg of ethinylestradiol for contraception. In order to achieve the essential reduction in the total contraceptive steroid administered per cycle, while maintaining good cycle

control, the low-dose progestogen/estrogen combination is administered for 23 to 25 days of a 28-day menstrual cycle. However, the patent does not disclose results and information proving that the inventive idea is also successful, and what is the desired mode of release of the steroids.

WO 01/015701 claims a pharmaceutical composition also for oral administration of 21 days of a 28-day menstrual cycle, which comprises drospirenone and ethinylestradiol, inter alia also in low doses, the drospirenone being present in micronized form. Particular attention is directed in this case at rapid release of the steroids.

EP 0 803 250 discloses a pharmaceutical tablet which has a pharmacologically active ingredient-free tablet core and whose outer sugar coating may comprise inter alia dienogest and ethinylestradiol and where the desired rapid release thereof is influenced by microcrystalline cellulose.

It is also known that it is absolutely necessary with low-dose oral contraceptives to pay attention to intake being in the same period each day. If this period is not complied with, the effective active ingredient concentration is below that necessary for oral contraception, and oral contraception is no longer ensured. This means that the user is required to keep track of her intake cycle very deliberately and with great care.

Detailed disclosure of the invention

The invention is based on the object of creating a possibility for reducing the conventional dienogest/ethinylestradiol active ingredient combination for oral contraceptives and at the same time ensuring contraceptive efficacy analogous to conventional oral contraceptives.

This object is achieved according to the invention by a solid oral pharmaceutical form for contraception which

comprises as active ingredient combination dienogest equal to or less than 2.0 mg and ethinylestradiol less than 0.030 mg, where the pharmaceutical form dienogest is released proportionately in at least two phases and of these at least one of the phases is released with a time delay relative to the other phase(s).

In the pharmaceutical form of the invention, preferably the dienogest has a rapid (non-slow) in vitro release within the first phase and a delayed (slow) in vitro release within the second phase and the ethinylestradiol has a conventional rapid in vitro release. The pharmaceutical form advantageously represents a tablet having a tablet core with a proportion, intended for slow release, of the total dienogest content and a coating with a proportion, intended for non-slow (rapid) release, of the total dienogest content and a total ethinylestradiol content intended for non-slow (rapid) release.

The tablet may be a film-coated tablet, in which case the coating is a film coating.

The pharmaceutical form according to the invention preferably comprises the active ingredient combination with 1.5 mg to 2.0 mg of dienogest and 0.015 mg to 0.020 mg of ethinylestradiol.

It is preferred for at least 10%, preferably 30% of dienogest to be slowly dissolved out of the tablet core after more than 30 minutes, as determined by the dissolution test with use of water at 37°C as dissolution medium and with a stirring speed of 50 rpm. The determination takes place in accordance with Ph. Eur. using a rotating basket apparatus with use of 1000 ml of water.

The dissolution of the proportion of dienogest and of the total ethinylestradiol content from the film coating is at least 75% in not more than 45 min, preferably 70% in 30 min, as determined by the dissolution test with use of water at 37°C as dissolution medium and with a stirring speed of 50 rpm.

It has been found that ethinylestradiol is stabilized

by ascorbic acid as soon as it is added to the active ingredient-containing film coating.

The proportion of ascorbic acid in this case is 0.02 to 1.0%, preferably 0.025 to 0.25%.

A preferred pharmaceutical form according to the invention constitutes the number of daily dose units which comprise the combination of dienogest and ethinylestradiol being 21, 22, 23, 24 or 25 and the number of daily dose units which comprise no active ingredient being 7, 6, 5, 4 or 3.

The release of the slow-release proportion of the dienogest active ingredient can be controlled by a large number of release-slowing principles. Examples of these release-slowing principles are inert plastics matrices, hydrocolloids, ion exchangers, slow-release coatings, gastro-resistant coatings, pellet mixtures, mixtures of minitablets and/or granules, microcapsules, osmotically controlled systems, erosion-controlled systems, diffusion-controlled systems and combinations thereof, fat- and wax-containing matrices.

The tablet forms shown in the examples are various embodiments of the pharmaceutical form according to the invention. The tablet forms such as oblong tablets are conceivable, as are tablet forms which in their configuration influence the erosion behaviour of hydrophilic matrices.

It has been found that, surprisingly, the partly delayed release of dienogest from the pharmaceutical form makes low dosage of the dienogest/ethinylestradiol active ingredient combination possible with the same contraceptive efficacy as conventional oral contraceptives comprising dienogest and ethinyl-estradiol, and ensures intake reliability without it being absolutely necessary to pay attention to intake being in the same period each day.

With suitable embodiments of the pharmaceutical product according to the invention, the number of daily dose units can be 21, 22, 23, 24 or 25 daily dose units, and the number of active ingredient-free daily dose units

is then 7, 6, 5, 4 or 3 in the 28-day menstrual cycle. Further embodiments with a number of daily dose units of 28 or a multiple of 28, for example 2 to 3 times 28, which comprise dienogest equal to or less than 2.0 mg and ethinylestradiol less than 0.030 mg are possible. Other embodiments with progestogens such as, for example, levonorgestrel, gestodene and others and/or estradiol valerate, which are suitable also for hormone replacement (also sequentially) besides contraception, are also possible.

The embodiments shown in the examples can also be varied in terms of the dosage. The proportion of dienogest in the second, slow-release phase ought preferably to be greater than 30% of the dienogest dose. This includes embodiments with 35%, 40%, 45%, 50% or 55%, but also for example 70%, 75%, 80% of the total dienogest dose. The time in which the proportion of dienogest in the second, slow-release phase is completely released varies in the examples from 180 min to 360 min. However, shorter or longer release times can also be achieved by variations of the examples.

Owing to the usual range of variation of active ingredient release, the release time is reported in whole hours, for example 1 h, 2 h, 3 h, 4 h as 6 h, 7 h etc.

It has emerged that the active ingredient combination in the pharmaceutical product according to the invention has, besides the contraception, antiandrogenic properties and therefore can be used in the prophylaxis and therapy of androgen-induced disorders, especially acne.

Brief description of the drawings

The invention is described in detail with reference to the following drawings, in which

Fig. 1 is a plot representing the release profile of Valette® with 2 mg of dienogest and 0.030 mg of

ethinylestradiol, produced and measured in accordance with Example 1;

Fig. 2 is a plot representing the release profiles of film-coated tablets with 2 mg of dienogest and 0.020 mg of ethinylestradiol, produced and measured in accordance with Examples 2 and 3;

Fig. 3 is a plot representing the release profiles of film-coated tablets with 1.5 mg of dienogest and 0.015 mg of ethinylestradiol, produced and measured in accordance with Example 8. The broken-line markings at 30 and 45 min clearly shows the release of proportions of dienogest in 2 phases, i.e. a slow release and a non-slow (rapid) release evident. A release behaviour of at least 75% of the active ingredient dose within not more than 45 min, preferably 70% in 30 min, is called rapid release.

Fig. 4 is a plot representing the release profile of a film-coated tablet with 1.5 mg of dienogest and 0.015 mg of ethinylestradiol in accordance with Example 8, variant 8.5 in analogy to variants 8.1 to 8.4.

Examples

Example 1

Description

Valette is a conventional sugar-coated tablet for oral contraception, comprising 0.030 mg of ethinylestradiol and 2.0 mg of dienogest in a tablet core which is covered with a sugar-containing sheath.

Test of the release profile

- Dissolution test of Ph. Eur., 4th edition, main volume 2002, 2.9.3, paddle stirrer apparatus, 50 rpm, dissolution medium 1000 ml of water
- Measurement of the amount of dienogest and ethinylestradiol released by high pressure liquid chromatography

Figure 1 shows the typical release profile of such contraceptive combinations of progestogen and estrogen to be evident. Such behaviour with release of at least

75% of the active ingredient dose within not more than 45 min, preferably of 70% in 30 min, is called fast release.

Example 2

2 mg of dienogest and 0.02 mg of ethinylestradiol, with delayed release of 1 mg of dienogest and fast release of 1 mg of dienogest and 0.02 mg of ethinylestradiol.

Description

The example describes a film-coated tablet with matrix core. The core of the film-coated tablet comprises 1 mg of dienogest in a hydrophilic erosion matrix with the basic ingredient Metolose. The active ingredient dienogest is released slowly from this matrix. The core was coated with a quickly dissolving film which comprises 1.0 mg of dienogest and 0.02 mg of ethinylestradiol. For protection from light, the film-coated tablet was coated with a further quickly dissolving coloured layer comprising iron oxide pigment.

Composition

Core		Film coating	
		Film 1 - active ingredient-containing	
Granules 1			
Dienogest	1.000 mg	Dienogest	1.000 mg
Metolose 90SH-4000	7.500 mg	Ethinylestradiol	0.020 mg
Lactose monohydrate	21.000 mg	Methocel 5	2.250 mg
Maize starch	14.000 mg	Talc	0.450 mg
Povidone K25 (10% in ethanol	1.500 mg	Titanium dioxide	0.280 mg
Granules 2		Film 2 - Coloured layer	
Lactose monohydrate	54.000 mg	Methocel 5	3.375 mg
Maize starch	27.100 mg	Talc	0.675 mg
Maltodextrin (25% in water)	6.900 mg	Titanium dioxide	1.875 mg
Outer phase		Iron oxide, red	0.075 mg
Carboxymethyl-starch sodium	1.500 mg		
Magnesium stearate	1.500 mg		

Production

- Granules 1: Dissolve povidone in ethanol and use this solution to granulate the other substances in a fluidized bed granulator
- Granules 2: Dissolve maltodextrin in water and use this solution to granulate the other substances in a fluidized bed granulator
- Mix granules 1, granules 2 and outer phase in a container mixer
- Convert mixture into tablets (136 mg, oblong punch 4.0×10.0 mm, curvature 4.5 mm)
- Film 1: Coat tablets with suspension of substances in water in a drum coater
- Film 2: Coat film-coated tablets with suspension of substances in water in a drum coater

Testing of the release profile

- Dissolution test of Ph. Eur., 4th edition, main volume 2002, 2.9.3, rotating basket apparatus, 50 rpm, dissolution medium 1000 ml of water
- Measurement of the amount of dienogest and ethinylestradiol released by high pressure liquid chromatography

Example 3

2 mg of dienogest and 0.02 mg of ethinylestradiol, with delayed release of 1 mg of dienogest and fast release of 1 mg of dienogest and 0.02 mg of ethinylestradiol.

Description

The example describes a film-coated tablet with matrix core. The core of the film-coated tablet comprises 1 mg of dienogest in a hydrophilic erosion matrix with the basic ingredient Metolose. The active ingredient dienogest is released slowly from this matrix. To avoid interactions between slow-release core and the active ingredient-containing film, the core was coated with a barrier layer before the active ingredient-containing film was applied. The active ingredient-containing film comprises 1.0 mg of dienogest and 0.02 mg of ethinylestradiol plus iron oxide pigments as protection

from light.

Composition

Core		Film coating	
Granules		Barrier layer	
Dienogest	1.000 mg	Opadry AMB white®	7.000 mg
Metolose 90SH-4000	7.500 mg	consisting of:	
Lactose monohydrate	31.000 mg	Polyvinyl alcohol - part hydrolysed	
Maize starch	24.000 mg	Titanium dioxide	
Povidone K25 (10% in ethanol	2.000 mg	Soya lecithin	
		Xanthan	
Outer phase		Active ingredient-containing film	
Tablettose	21.000 mg	Dienogest	1.000 mg
Avicel PH 102	16.200 mg	Ethinylestradiol	0.020 mg
Magnesium stearate	1.300 mg	Methocel 5	2.250 mg
		Talc	0.430 mg
		Titanium dioxide	0.280 mg
		Iron oxide, red	0.020 mg

Production

- Granules: Dissolve povidone in ethanol and use this solution to granulate the other substances in a fluidized bed granulator
- Mix granules 1 and outer phase in a container mixer
- Convert mixture into tablets (104 mg, oblong punch 4.0×10.0 mm, curvature 4.5 mm)
- Barrier layer: Coat tablets with suspension of substances in water in a drum coater
- Active ingredient-containing film: Coat film-coated tablets with suspension of substances in water in a drum coater

Testing of the release profile

- Dissolution test of Ph. Eur., 4th edition, main volume 2002, 2.9.3, rotating basket apparatus, 50 rpm, dissolution medium 1000 ml of water
- Measurement of the amount of dienogest and

ethinylestradiol released by high pressure liquid chromatography

The film-coated tablets of Examples 2 and 3 differ in the structure of the film coating. The active ingredient-containing film dissolves rapidly and quickly releases the ethinylestradiol dose and the proportion of the dienogest dose. The coloured layer in Example 2 likewise dissolves rapidly. It ensures that the film-coated tablet is acceptable and protected from light. The barrier layer in Example 3 suppresses interactions between active ingredient-containing film and the core and dissolves more slowly than the active ingredient-containing film. Both film-coated tablets have a matrix core consisting of a hydrophilic erosion matrix. This erosion matrix slowly releases the slow-release portion of the dienogest dose.

Figure 2 shows the measured release profiles of Examples 2 and 3 shown. The film-coated tablets of both examples release about 80% of the ethinylestradiol dose within 45 min and about 50% of the dienogest dose within 45 min. The remaining proportion of the dienogest dose is released within 360 min in the film-coated tablet from Example 2 and within 180 min in the case of Example 3.

Example 4

In Example 4, the release of the slow-release proportion of dienogest is controlled with a lipophilic matrix.

Description

The example describes a tablet comprising 2 mg of dienogest and 0.020 mg of ethinylestradiol with a lipophilic release-slowing principle. 1 mg of dienogest is incorporated into a lipophilic matrix by spraying. The fast-release proportion of dienogest and the ethinylestradiol are admixed with this matrix.

Composition

Dienogest (in ethanolic solution)	1.00 mg
Cetylstearyl alcohol (in ethanolic solution)	9.00 mg
Lactose monohydrate	57.98 mg
Maize starch	10.00 mg
Dienogest	1.00 mg
Ethinylestradiol	0.02 mg
Maltodextrin (20% solution in water)	9.00 mg
Na carboxymethylstarch	1.00 mg
Magnesium stearate	1.00 mg

Production

- Dissolve slow-release proportion of dienogest and cetylstearyl alcohol in ethanol at 50°C
- Spray dienogest/cetylstearyl cohol solution onto lactose and maize starch in fluidized bed granules, and dry
- Admix ethinylestradiol, 2nd half of the dienogest dose dry
- Dissolve maltodextrin in water
- Granulate mixture in the fluidized bed with maltodextrin solution
- Admix Na carboxymethylstarch and magnesium stearate
- Tablet to give tablets of diameter 5.5 mm and mass 90 mg

Example 5

In Example 5, the release of dienogest is controlled by use of different particle sizes.

Description

The example describes a tablet in which dienogest is employed with different particle fractions. Targeted adjustment of the particle size takes place by fractional crystallization.

Composition

Dienogest (average particle size 3 µm)	0.667 mg
Dienogest (average particle size 180 µm)	0.667 mg
Dienogest (average particle size 270 µm)	0.667 mg
Ethinylestradiol	0.02 mg
Lactose monohydrate	47.18 mg
Maize starch	24.00 mg
Maltodextrin (20% solution in water)	9.00 mg
Magnesium stearate	0.80 mg

Production:

- Granulate the substances with maltodextrin solution
- Dry the granules
- Admix magnesium stearate
- Convert mixture into tablets (diameter 5.5 mm with mass 80 mg)

Example 6

A chemical problem arises when the ethinylestradiol dose is reduced. The increase in dilution of the active ingredient in the pharmaceutical form speeds up its chemical decomposition during storage, possibly even during production of the pharmaceutical form. Surprisingly, ascorbic acid has emerged as effective stabilizer for ethinylestradiol. Example 6 shows the efficacy of ascorbic acid as stabilizer in formulation examples.

Description

The example describes the stabilizing effect of ascorbic acid on ethinylestradiol by means of formulation examples in a stress test.

Composition

Variant	6.1	6.2	6.3	6.4	6.5
Ascorbic acid, in binder solution	-	0.02 mg	0.20 mg	-	-
Ascorbic acid, in mixture	-	-	-	0.02 mg	0.20 mg
Dienogest	2.00 mg	2.00 mg	2.00 mg	2.00 mg	2.00 mg
Ethinyl-estradiol	0.02 mg	0.02 mg	0.02 mg	0.02 mg	0.02 mg
Lactose monohydrate	47.18 mg	47.16 mg	46.98 mg	47.16 mg	46.98 mg
Maize starch	24.00 mg	24.00 mg	24.00 mg	24.00 mg	24.00 mg
Maltodextrin	6.00 mg	6.00 mg	6.00 mg	6.00 mg	6.00 mg
Magnesium stearate	0.80 mg	0.80 mg	0.80 mg	0.80 mg	0.80 mg

Production

- Mix lactose, maize starch and dienogest in a granulator, spray with a solution of ethinylestradiol in ethanol, and dry
- Granulate mixture with maltodextrin binder solution in water, dry and mix with magnesium stearate
- Tablet mixture to give tablets of mass 80 mg and diameter 5.5 mm

Test of the content in a stress test

The tablets are stored in an open vessel at 60°C and 80% relative humidity. After the storage time of 42 days has elapsed, the tablets are removed and investigated. The ethinylestradiol content is measured by HPLC and set in relation to the initial content.

Variant	6.1	6.2	6.3	6.4	6.5
Ascorbic acid, in binder solution	-	0.02 mg	0.20 mg	-	-
Ascorbic acid, in mixture	-	-	-	0.02 mg	0.20 mg
Content after 42 days	79.1%	90.1%	91.9%	91.6%	96.5%

Example 7

Description

In this example, the stabilization of ethinylestradiol in the active ingredient-containing layer of film-coated tablets is described.

Composition

Core	104 mg
Dienogest	0.750 mg
Metolose 90SH-4000	7.500 mg
Lactose monohydrate	45.250 mg
Maize starch	10.000 mg
Povidone K25 (10% in water)	2.000 mg
Tablettose	30.000 mg
Avicel PH 102	7.200 mg
Magnesium stearate	1.300 mg
Barrier layer	6 mg
Eudragit RL 30 D (as coating dry matter)	3.500 mg
Macrogol 6000	0.700 mg
Talc	1.800 mg
Active ingredient-containing film	3 mg
Dienogest	0.750 mg
Ethinylestradiol	0.015 mg
Ascorbic acid	0.200 mg
Methocel 5	1.6875 mg
Talc	0.2375 mg

Titanium dioxide	0.210 mg
Coloured layer	3 mg
Methocel 5	1.500 mg
PEG 6000	0.300 mg
Talc	0.300 mg
Titanium dioxide	0.850 mg
Iron oxide, red	0.050 mg

Production

- Dienogest, Metolose 90SH-4000, lactose monohydrate and maize starch are granulated with the aqueous povidone K25 and maltodextrin solution
- Tablettose, Avicel PH 102 and magnesium stearate are admixed with the dry granules
- The mixture is tabletted
- The tablets are coated with the appropriate films in a drum coater

Example 8

Description

Five variants of film-coated tablets with a total dose of 1.5 mg of dienogest and 0.015 mg of ethinylestradiol are described. The film-coated tablets consist of a slow-release matrix core and a quickly dissolving film coating and of a coloured layer. In two variants, a barrier layer was additionally provided between core and active ingredient-containing film.

In the five variants of the film-coated tablet, the slow-release proportion of the dienogest dose was varied in the range from 33% to 66%. The formulation of the core was adapted to the desired release profiles.

Composition

Variant	8.1	8.2	8.3	8.4
Core	104 mg	104 mg	104 mg	104 mg
Dienogest	0.750 mg	0.500 mg	1.000 mg	0.750 mg
Metolose 90SH-4000	7.500 mg	7.500 mg	7.500 mg	9.000 mg
Lactose monohydrate	45.250 mg	39.500 mg	45.000 mg	29.750 mg
Maize starch	10.000 mg	10.000 mg	10.000 mg	24.000 mg
Povidone K25 (10%	2.000 mg	-	2.000 mg	2.000 mg
in water)	-	8.000 mg	-	-
Maltodextrin (25%	30.000 mg	30.000 mg	30.000 mg	21.000 mg
in water)	7.200 mg	7.200 mg	7.200 mg	16.200 mg
Tablettose	1.300 mg	1.300 mg	1.300 mg	1.300 mg
Avicel PH 102				
Magnesium stearate				
Barrier layer	6 mg	6 mg	-	-
Eudragit RL 30 D	3.500 mg	3.500 mg		
(as coating dry				
matter)	0.700 mg	0.700 mg		
Macrogol 6000	1.800 mg	1.800 mg		
Talc				
Active ingredient-containing film	3 mg	3 mg	3 mg	3 mg
Dienogest	0.750 mg	1.000 mg	0.500 mg	0.750 mg
Ethinylestradiol	0.015 mg	0.015 mg	0.015 mg	0.015 mg
Methocel 5	1.6875 mg	1.4987 mg	1.8848 mg	1.6875 mg
Talc	0.3375 mg	0.2998 mg	0.3700 mg	0.3375 mg
Titanium dioxide	0.210 mg	0.18650 mg	0.2302 mg	0.210 mg
Coloured layer	3 mg	3 mg	3 mg	3 mg
Methocel 5	1.500 mg	1.500 mg	1.500 mg	1.500 mg
PEG 6000	0.300 mg	0.300 mg	0.300 mg	0.300 mg
Talc	0.300 mg	0.300 mg	0.300 mg	0.300 mg
Titanium dioxide	0.850 mg	0.850 mg	0.850 mg	0.850 mg
Iron oxide, red	0.050 mg	0.050 mg	0.050 mg	0.050 mg

Example 8 -variant 8.5

Composition

Variant	8.5
Core	104 mg
Dienogest	0.675 mg
Metolose 90SH-4000	9.000 mg
Lactose monohydrate	42.925 mg
Maize starch	15.000 mg
Povidone K25 (10% in water)	
Maltodextrin (25% in water)	6.000 mg
Tablettose	8.500 mg
Avicel PH 102	7.000 mg
Magnesium stearate	0.900 mg
Barrier layer	-
Eudragit RL 30 D (as coating dry matter)	
Macrogol 6000	
Talc	
Active ingredient-containing film	
Dienogest	0.825 mg
Ethinylestradiol	0.015 mg
Methocel 5	4.060 mg
Talc	0.836 mg
Titanium dioxide	0.264 mg
Coloured layer	
Methocel 5	1.500 mg
PEG= Macrogol 6000	0.300 mg
Talc	0.300 mg
Titanium dioxide	0.850 mg
Iron oxide, red	0.050 mg

5 Production

- Dienogest, Metolose 90SH-4000, lactose monohydrate and maize starch are granulated with the aqueous povidone K25 and maltodextrin solution
- Tablettose, Avicel PH 102 and magnesium stearate

are admixed with the dry granules

- The mixture is tabletted
- The tablets are coated with the appropriate films in a drum coater

Testing of the release profile

- Dissolution test of Ph. Eur., 4th edition, main volume 2002, 2.9.3, rotating basket apparatus, 50 rpm, dissolution medium 1000 ml of water
- Measurement of the amount of dienogest and ethinylestradiol released by high pressure liquid chromatography

Example 9

Variants of film-coated tablets with a total dose of 2.0 mg of dienogest and 0.015 mg of ethinylestradiol are described, produced and tested in analogy to the variants in Example 8.

The contraceptive efficacy of formulations comprising dienogest and ethinylestradiol can be demonstrated in investigations, for example in a randomized open clinical study. This entails various biochemical and function-testing investigations being carried out. To detect the ovulation-inhibiting effect, FSH, LH, estradiol, progesterone, "spinnbarkeit" and ferning are investigated. Follicle maturation is examined by means of an ultrasound investigation. In addition, SHBG, CBG, total testosterone, triglycerides, cholesterol, HDL, LDL, glucose in serum are determined, and blood pressure, heart rate, body weight and bleeding behaviour are recorded.

Claims

1. Solid oral pharmaceutical form for contraception, comprising 17α-cyanomethyl-17-β-hydroxyestra-4,9-dien-3-one (dienogest) equal to or less than 2.0 mg and 17α-ethinylestradiol (ethinylestradiol) less than 0.030 mg, where the dienogest is released proportionately in at least two phases and of these at least one of the phases is released with a time delay relative to the other phase(s).

2. Pharmaceutical form according to Claim 1 with a proportion, intended for slow release, of the total dienogest content and a proportion, intended for non-slow (rapid) release, of the total dienogest content.

3. Pharmaceutical form according to either of Claims 1 and 2 with a proportion, intended for slow release, of the total dienogest content and a proportion, intended for non-slow (rapid) release, of the total dienogest content and a total ethinylestradiol content intended for non-slow (rapid) release.

4. Pharmaceutical form according to either of Claims 1 and 3, where the pharmaceutical form represents a tablet having a tablet core with a proportion, intended for slow release, of the total dienogest content and a coating with a proportion, intended for non-slow (rapid) release, of the total dienogest content and a total ethinylestradiol content intended for non-slow (rapid) release.

5. Pharmaceutical form according to Claim 4, comprising as active ingredient combination dienogest equal to or less than 2.0 mg and ethinylestradiol less than 0.030 mg, where the

pharmaceutical form represents a film-coated tablet with a tablet core with a proportion, intended for slow release, of the total dienogest content and a film coating with a proportion, intended for non-slow (rapid) release, of the total dienogest content and a total ethinylestradiol content intended for non-slow (rapid) release.

6. Pharmaceutical form according to any of Claims 1 to 5, where the active ingredient combination comprises 1.5 mg to 2.0 mg of dienogest and 0.015 mg to 0.020 mg of ethinylestradiol.

7. Pharmaceutical form according to any of Claims 1 to 6, where at least 10%, preferably 30% of dienogest are slowly dissolved out of the tablet core after more than 30 minutes as determined with the dissolution test with use of water at 37°C as dissolution medium and 50 rpm as stirring speed.

8. Pharmaceutical form according to any of Claims 1 to 7, where ascorbic acid is added as stabilizer of the ethinylestradiol to the active ingredient-containing film coating.

9. Pharmaceutical form according to Claim 8, where the proportion of ascorbic acid is 0.02 to 1.0%, preferably 0.025 to 0.25%.

10. Pharmaceutical form according to any of Claims 1 to 9, where the number of daily dose units comprising the combination of dienogest and ethinylestradiol is 21, 22, 23, 24 or 25, and the number of daily dose units comprising no active ingredient is 7, 6, 5, 4 or 3.