# Multi-phase contraceptive preparation based on a natural estrogen

## Description

### Technical Field

The invention relates to a multiphase product for contraception based on a natural oestrogen with a synthetic progestogen.

Compared with the generic conventional ovulation-inhibiting products which have proved to be reliable and safe on wide use for a long time, this multiphase product achieves a greater contraceptive reliability over the entire duration of the cycle, improves the cyclic bleeding behaviour and minimizes or eliminates side effects such as breast tenderness, headaches, depressive moods and libido changes and the like.

### Prior Art

The patent literature discloses multiphase products based on natural oestrogens in combination with progestogens.

The patent EP 0 770 388 B1 describes a multiphase product for contraception whose first phase consists of 2 to 4 daily dose units, and each daily dose unit contains as active ingredient exclusively natural oestrogens. The second phase of the multiphase product consists of 2 groups of daily dose units with a combination of at least one natural oestrogen and at least one synthetic or natural progestogen. In this case, the first group is formed by 5 to 3 daily dose units and the second group is formed by 17 to 13 daily dose units. A third phase consists of 2 to 4 daily dose units, and each daily dose unit contains as active ingredient exclusively natural oestrogens. The daily dose unit of natural oestrogen remains constant within the phases, but falls from phase 1 to phase 3. The proportion of synthetic or natural progestogen in the

second group of the second phase exceeds the proportion in the first group. A final phase consists of 2 to 4 daily dose units, and each daily dose unit contains as active ingredient a pharmaceutically acceptable placebo.

Use example 5 indicates a combination of oestradiol valerate with dienogest. In this case, in the first phase 3 daily dose units of 3 mg of oestradiol valerate, in the second phase, in the first group, 4 daily dose units of 2 mg of oestradiol valerate plus 1 mg of dienogest, in the second group of this second phase 16 daily dose units of 2 mg of oestradiol valerate plus 2 mg of dienogest and in the third phase 2 daily dose units of 1 mg of oestradiol valerate are administered. The last phase contains 3 daily dose units of pharmaceutically acceptable placebo.

For information on contraceptive reliability, the progesterone serum concentration was measured radio-immunologically. A limit of 4.0 ng/ml progesterone has been stated. The average rate of irregular bleeding (breakthrough bleeding and spotting) fell by 45 to 53% from the first intake cycle to the last intake cycle.

It is additionally known that the contraceptive reliability of combination products derives from the effect of both components, of the oestrogen and of the progestogen.

It is also known that the ovulation-inhibitory dose requires 1.0 mg a day for dienogest - Dienogest: Präklinik und Klinik eines neuen Gestagens, edited by A.T. Teichmann, Walter de Gruyter Berlin/New York (1995), p. 101) and 2.0-3.0 mg for drospirenone (Rosenbaum P, Schmidt W, Helmerhorst F M et al., Inhibition of ovulation by a novel progestogen (drospirenone)..., Eur contracept. Reprod. Health Care 5: 16-24 (2000)).

Moreover, TAUBERT, H.-D. and KUHL, H. (Kontrazeption mit Hormonen, editors Taubert, H.-D. et al., Georg Thieme Verlag Stuttgart/New York (1995), p. 160) show that there is no connection whatsoever between the occurrence of irregular bleeding and low serum concentrations of the oestrogen, in this case ethinyl-oestradiol, or of the particular progestogen.

**Field of the Invention**

It is consequently an object of the invention to indicate a composition for hormonal contraception based on a natural oestrogen which, compared with the generic conventional ovulation-inhibiting compositions based on natural oestrogens, achieves a greater contraceptive reliability over the entire duration of the cycle, improves the cyclic bleeding behaviour, and controls side effects such as breast tenderness, headaches, depressive moods and libido changes and the like. This object is achieved according to the invention by a multiphase product for contraception, whose first phase consists of 2 daily dose units of 3 mg of the natural oestrogen oestradiol valerate. A second phase consists of 2 groups of daily dose units, where a the first group contains 5 daily dose units of a combination of 2 mg of oestradiol valerate and at least twice or three times the ovulation-inhibitory dose of a synthetic progestogen. The second group of the second phase consists of 17 daily dose units of a combination of 2 mg of oestradiol valerate and at least three times or four times the ovulation inhibitory does of a synthetic progestogen. A third phase contains 2 daily dose units with 1 mg of oestradiol valerate and a further phase 2 daily dose units of pharmaceutically acceptable placebo.

As synthetic progestational active ingredient, use may advantageously be made of dienogest, drospirenone or a progestogen at at least twice its known ovulation-inhibitory dose.

at least three times or four times the ovulation-inhibiting dose of a synthetic progestogen. A third phase comprises 2 daily dose units with 1 mg of oestradiol valerate, and *a* further phase comprises 2 daily dose units of pharmaceutically acceptable placebo.

It is advantageously possible to employ as synthetic progestational active ingredient dienogest, drospirenone or a progestogen with at least twice its known ovulation-inhibiting dose. It is also possible to employ as progestational active ingredients substances of the 19-nortestosterone derivatives such as levonorgestrel, gestodene, norgestimate, desogestrel and norethisterone and its derivatives such as norethisterone acetate and norethisterone enanthate, and substances of the C-21-progestogens such as chlormadinone acetate, cyproterone acetate and medroxyprogesterone acetate.

The multiphase product according to the invention is particularly suitable for oral administration, but intravaginal, parenteral, including topical, rectal, intranasal, intrabuccal or sublingual administrations are also conceivable as dosage forms.

The multiphase product is produced with the conventional solid or liquid carriers or diluents and the excipients conventionally used in pharmaceutical technology appropriate for the desired mode of administration with a suitable dosage in a known manner.

Tablets, film-coated tablets, sugar-coated tablets or hard gelatin capsules are preferably used for oral administration.

**Exemplary embodiments**

The invention is to be demonstrated by some examples of use. In this connection, in particular the contraceptive reliability, the cyclic bleeding behaviour of the woman, and the tolerability of the administration regimen is demonstrated.

**Contraceptive reliability**

The contraceptive reliability was demonstrated in principle by determining the Hoogland score which uses the follicle size, the oestradiol level and progesterone values. In the present case, the progesterone serum concentration was measured radio-immunologically on selected days of the cycle, and the number of ovulations (Hoogland score 6) and of luteinized, non-ruptured follicles (Hoogland score 5) was determined.

**Cycle stability**

The cycle stability was assessed on the basis of a bleeding pattern recorded for each cycle. Of particular interest in this connection was the occurrence of

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**Cycle stability**

The cycle stability was assessed on the basis of a bleeding pattern recorded for each cycle. Of particular interest in this connection was the occurrence of

irregular bleeding (spotting or breakthrough bleeding). The mode of recording was standardized. The data were analysed descriptively.

**Tolerability**

The tolerability was tested on the basis of subjective feelings such as headaches, depressive moods, breast tenderness, gastric upsets (nausea/vomiting), oedemas and libido changes.

**Use Example 1**

The following regimen was used:

| | |
|---|---|
| days 1 to 2 | 3 mg of oestradiol valerate/d |
| days 3 to 7 | 2 mg of oestradiol valerate/d + 2 mg of dienogest/d |
| days 8 to 24 | 2 mg of oestradiol valerate/d + 3 mg of dienogest/d |
| days 25 to 26 | 1 mg of oestradiol valerate/d |
| days 27 to 28 | placebo |

The study was carried out on 93 female subjects 18 to 35 years old. The duration of intake amounted to 3 cycles in each case, with only cycles 2 and 3 being observed.

In the 2nd cycle (primary target variable), 3 of 93 women (3.23%) ovulated, and 2 of 92 women in the 3rd cycle.

It was thus possible to record reliable inhibition of ovulation in 96.77% on use of the administration regimen according to the invention.

At the same time, good tolerability is found on intake of the administration regimen according to the invention.

**Use Example 2**

| | | |
|---|---|---|
| days | 1 to 2 | 3 nag of oestradiol valerate/d |
| days | 3 to 7 | 2 mg of oestradiol valerate/d + 3 mg of dienogest/d |
| days | 8 to 24 | 2 mg of oestradiol valerate/d + 4 mg of dienogest/d |
| days | 25 to 26 | 1 mg of oestradiol valerate/d |
| days | 27 to 28 | placebo |

The study was carried out on 93 female subjects 18 to 35 years old. The duration of intake amounted to 3 cycles in each case, with only cycles 2 and 3 being observed.

In the 2nd cycle (primary target variable), 2 of 93 women (2.15%) ovulated, and 2 of 92 women in the 3rd cycle.

It was thus possible to record reliable inhibition of ovulation in 97.85% on use of the administration regimen according to the invention.

At the same time, good tolerability is found on intake of the administration regimen according to the invention.

It is possible with the two use examples to record an adequate inhibition of ovulation of respectively 97.85% and 96.77%. Very recent investigations with conventional ovulation inhibitors by Pierson R A et al., "Ortho Evra/Evra versus oral contraceptives: follicular development...", Fertil. Steril. 80(1), pp. 34-42 (2003) demonstrate ovulation in a certain percentage even with products which have proved to be reliable and safe on wide use for a long time. In the second treatment cycle it was possible to observe ovulations for example with a three-phase levonorgestrel-containing oral contraceptive in 14% (3

of 22), with a monophasic levonorgestrel-containing oral contraceptive (6 of 25) and with a triphasic norgestimate-containing oral contraceptive in 16% (4 of 25). These values are distinctly above those for the products according to the invention, so that a higher reliability can be expected with these compared with Pierson et al.