PHARMACEUTICAL PREPARATION FOR THE ALLEVIATION OF ENDOMETRIOSIS

Technical field

The invention relates to a pharmaceutical composition for lessening endometriosis without reducing the bone density, which comprises a progestogen having antiandrogenic activity in a daily dose which does not exceed twice the ovulation-inhibitory dose, together with one or more pharmaceutically acceptable excipients/carriers. The invention also embodies a monophasic product which has no negative effect on bone metabolism. This product is therefore suitable for long-term use. Nevertheless, the use of progestogens having antiandrogenic activity in the above dose for manufacturing a pharmaceutical product for the prophylaxis and/or therapy of endometriosis without a negative effect on bone metabolism and thus a reduction in bone density makes it possible to keep the side effects known for conventional pharmaceutical compositions, such as, for example, hot flushes, acne, alteration in the lipid profile, within tolerable limits.

Prior art

Endometriosis is a chronic gynecological disorder occurring primarily in 5-20% of women of childbearing age. Endometriosis is defined in the specialist literature as the occurrence of endometrium or endometrium-like tissue outside the cavity of the uterus. Typical symptoms of the endometriotic disorder are dysmenorrhea, dyspareunia and pain on defecation. Endometriosis patients frequently complain of pain in the pelvic region. Lower abdominal pain occurring in the 2nd half of the cycle, followed by a painful period and subsequent freedom from symptoms until the middle

of the following cycle, frequently suggest an endometriotic disorder, but permanent pain is not uncommon either. However, about 30-40% of patients with endometriosis have no symptoms. The disorder is then found only by chance in connection with other diagnostic measures. In about 50-60%, the diagnosis "suffering from endometriosis" is made as a chance diagnosis when seeking an explanation for sterility.

It is known from the specialist and patent literature to treat endometriosis medically with danazole, a derivative of 17α-ethynyltestosterone, GnRH agonists, progestogen/estrogen combinations or progestogen-alone products.

US 6,569,845 discloses the treatment of angiogenic disorders with dienogest in a daily dose of 0.5 to 10 mg. Corresponding pharmaceutical compositions provided as examples, which could also be widely used for the treatment of endometriosis, have a dienogest content of 400 mg to 2 g.

Moore, C. *et al.*, The treatment of endometriosis, Drugs of Today 1999, 35 (Suppl C): 41-52 investigated the efficacy of dienogest in the treatment of endometriosis in clinical studies compared with the treatment regimen with danazole or GnRH agonists. 2 mg of dienogest were administered each day for 24 weeks to those affected by endometriosis. The result of the treatment is comparable with the result of a treatment with danazole or GnRH agonists. Up to 90% of those affected reported irregular bleeding, but none reported intolerable bleeding. The efficacy of the standard treatment with danazole is curtailed by significant androgenic effects, whereas GnRH agonists are connected with "menopausal symptoms".

Schweppe, K.-W, Stellenwert der Gestagene, Zentralbl

Gynakol 2003, 125: 276-280 states that low estrogen levels are to be found on continuous oral progestogen treatment (for example with medroxyprogesterone acetate, dienogest, dydrogesterone, lynestrenol in a daily dose of 5 mg to 20 mg, referred to as low-dose and categorized as effective principle for treating endometriosis-related symptoms). Spotting and irregular bleeding are frequent results. This forces an increase in the dose and/or addition of estrogen. Recurrence rates long-term are above 50%.

A safety data sheet of 2005 on a medroxyprogesterone acetate product indicates that progestogen-alone products may exert an adverse effect on bone density, especially on long-term treatment. By contrast, some progestogens combined with estrogens exert a positive influence on bone metabolism.

A further safety data sheet, NDA 21-584, FDA 22.03.2005, on depo-subQ provera 104™ (medroxyprogesterone acetate i.m. - 104 mg/0.65 ml) indicates that women using this product suffer a loss of bone mineral density which increases with the duration of use of the product and is no longer completely reversible.

Knauthe, R and Habenicht U.F., Levonorgestrel has beneficial effects, Exp Clin Endocrinol diabetes 106 (1998) Suppl 1: 37 showed in 1998 that in this connection the partial androgenic effect of a progestogen (levonorgestrel) and not the progestational activity is decisive for this positive influence on bone metabolism. Moreover, Kuhl, H., Klimakterium, Postmenopause und Hormonsubstitution, 3rd edition, Bremen, UNI-MED, 2006, 117 emphasizes that certain progestogens are effective via their partial androgenic effect. Kuhl further states that androgens considerably enhance the positive effect of estrogens on bone

density.

Description of the invention

The object of the invention is a pharmaceutical composition having a steroidal content which is as low as possible for lessening endometriosis, the intention being that the composition does not at the same time exert a negative influence on bone density/bone metabolism.

It has now been found that it is possible to achieve alleviation of endometriosis without reducing the bone density by a pharmaceutical composition with a low hormonal dosage, specifically a progestogen having antiandrogenic activity whose daily dose does not exceed twice the ovulation-inhibitory dose, and one or more pharmaceutically acceptable excipients/carriers.

At the same time, the pharmaceutical composition and use thereof or the corresponding monophasic product, besides alleviating endometriosis, surprisingly achieves no negative influence on bone metabolism, so that no decrease/reduction in bone density is to be found.

Nevertheless, the pharmaceutical composition and the use thereof or the corresponding monophasic product surprisingly keeps the side effects known for conventional medicaments for the treatment of endometriosis, e.g. hot flushes, alteration in the lipid profile, within tolerable limits.

The progestogens having antiandrogenic activity which are used according to the invention are dienogest, cyproterone acetate or chlormadinone acetate.

The daily dose of dienogest not exceeding twice the

ovulation-inhibitory dose does not exceed 2 mg. Cyproterone acetate or chlormadinone acetate are also employed according to the invention in a daily dosage not exceeding twice the ovulation-inhibitory dose. The ovulation-inhibitory dose of dienogest and of cyproterone acetate is 1 mg, and that of chlormadinone acetate is 1.7 mg.

The daily dose of the progestogens may be once not more than twice the ovulation-inhibitory dose or twice the same dose not exceeding half the ovulation-inhibitory dose.

The object is also achieved according to the invention by a pharmaceutical composition comprising daily dose units which are packed separately and can be removed singly and which are introduced into a pack unit for a period of 28 or 30 consecutive days, where the daily dose units comprise not more than 2 mg of dienogest or an equivalent amount of cyproterone acetate or chlormadinone acetate together with one or more pharmaceutically acceptable excipients/carriers.

The pack units are preferably 2 blister packs each with 14 or 15 daily dose units.

It has been found that the pharmaceutical composition, which is suitable for the prophylaxis and/or therapy of endometriosis, surprisingly exerts no negative effect on bone metabolism and bone density, and the lipid profile. The pharmaceutical composition is therefore surprisingly suitable for long-term administration, especially with a continuous administration of the dosage forms for a period of at least 169 days or 25 weeks up to several years, preferably more than 2 years.

The object is also achieved according to the invention

by a kit which comprises at least 28, preferably 30, daily dose units not exceeding twice the ovulation-inhibitory dose of a progestogen having a partial antiandrogenic effect, preferably dienogest, cyproterone acetate or chlormadinone acetate, together with one or more pharmaceutically acceptable excipients/carriers.

The present invention further relates to the use of progestogens having antiandrogenic activity in a daily dose which does not exceed twice the ovulation-inhibitory dose for manufacturing a pharmaceutical product for the prophylaxis and/or therapy of endometriosis, it having been found that, surprisingly, no negative influence on bone metabolism, and thus no decrease in bone density, is to be found. At the same time, the side effects known for conventional medicaments for the treatment of endometriosis, e.g. hot flushes, alteration in the lipid profile, are kept within tolerable limits.

Further embodiments of the invention are evident from the features of dependent claims 9, 10, 11 or 12.

The pharmaceutical product may be in the form of tablets, capsules, coated tablets, wafers, transdermal therapeutic systems, ampoules, suppositories, gels, ointments, implants, vaginal rings or nasal spray. In this connection, the daily dose of progestogen delivered by the non-oral forms of the pharmaceutical product, such as transdermal therapeutic system, ampoule, suppository, gel, ointment, implant, vaginal ring or nasal spray, is equivalent to the daily dose unit not exceeding twice the ovulation-inhibitory dose for the oral forms.

The invention further relates to a monophasic product for alleviating endometriosis which includes at least

28 dosage units, preferably 30 dosage units, where appropriate in each case 2 blister packs of 14 or 15 dosage units, each comprising a progestogen having antiandrogenic activity with not more than twice the ovulation-inhibitory dose, selected from dienogest, cyproterone acetate or chlormadinone acetate.

The invention also relates to a monophasic product for alleviating endometriosis and without a negative influence on bone metabolism and thus a reduction in bone density which includes the above dosage units, each comprising a progestogen having antiandrogenic activity with not more than twice the ovulation-inhibitory dose, selected from dienogest, cyproterone acetate or chlormadinone acetate, where the dosage units are administered continuously for at least 169 to more than 730 days.

The monophasic product is suitable for the prophylaxis and/or therapy of endometriosis, and lessens endometriosis, but does not have a negative influence on bone metabolism/bone density and keeps both the known side effects related to endometriosis therapy (reduced bone density, hot flushes, altered lipid profile) within tolerable limits. It is therefore suitable for long-term therapy.

Exemplary embodiments

Example 1

Tablets with the following composition are produced:

Dienogest, micronized min. 99% ≤ 20 µm, 100% < 30 µm	2,000 mg
Lactose monohydrate	62,800 mg
Microcrystalline cellulose	18,000 mg
Potato starch	36,000 mg

Povidone K 25	8,100 mg
Magnesium stearate	1,350 mg
Talc	4,050 mg
Crospovidone	2,700 mg

Dienogest is employed micronized with an average particle size of 20 µm and mixed with lactose monohydrate, microcrystalline cellulose and potato starch. The povidone K 25 is sprayed in during the granulation. After drying and admixing of talc, crospovidone and magnesium stearate, the mixture of substances is compressed to tablets with a diameter of 7 mm and a mass of 135 mg.

Example 2

In a clinical study, 252 women with endometriosis diagnosed at laparoscopy were treated over a period of 6 months either with the GnRH agonist leuprorelin acetate (LA) 3.75 mg s.c. every 4 weeks or with 2 mg/d of the progestogen dienogest (DNG) orally. 128 patients were randomized to the LH group and 124 patients to the DNG group. The efficacy of the respective therapy was examined inter alia by means of a scale of pain (visual analogue scale, VAS) to be completed by the patient. At the end of the treatment, both comparison groups showed a similar reduction in pain compared with the start of the study (-47.5 mm for DNG; -46.0 mm for LA). Statistical analysis showed non-superiority of DNG over LA.

In addition, common side effects of hormonal therapy methods for endometriosis were recorded:

Alterations in the menstrual bleeding occurred in both treatment groups, frequently as absence of period or in the form of slightly irregular bleeding - but these led to discontinuation of the therapy in only a few

patients.

Hot flushes, a typical symptom of estrogen deficiency, occurred substantially less often in the DNG group (0.89 days with hot flushes/week) than in the LH group (4.23 days/week). In addition, the symptoms in the DNG group declined during the 6-month therapy, whereas they increased with LA.

The influence of the two therapies on bone metabolism was examined in a subgroup of patients. At the end of the 6-month therapy, there was found to be a statistically significant difference in favor of DNG: with DNG, the bone density was virtually unchanged by comparison with the start of the study (+0.25%), whereas a distinct fall (-4.0%) had occurred in the comparison group. These results were confirmed by laboratory parameters for determining bone metabolism, which indicated an increased bone resorption during therapy with LA.

The estrogen levels were substantially unchanged during therapy with DNG (average before therapy: 256.3 pmol/l; end of study: 249.9 pmol/l), whereas there was a distinct fall with LA (before therapy: 299.0 pmol/l; end of study: 68.5 pmol/l). The other laboratory investigations concerning safety did not reveal any significant changes in either of the two treatment groups.

Overall, the two treatments were equivalent in terms of the efficacy, whereas DNG showed distinct advantages in terms of the side effects related to estrogen deficiency, such as hot flushes and reduced bone density.

Claims

1. A pharmaceutical composition for lessening endometriosis and without a negative influence on bone metabolism and thus a reduction in bone density, comprising a progestogen having antiandrogenic activity in a daily dose not exceeding twice the ovulation-inhibitory dose, together with one or more pharmaceutically acceptable excipients/carriers.

2. The pharmaceutical composition as claimed in claim 1, characterized in that the progestogen component is 17α-cyanomethyl-17-β-hydroxyestra-4,9-dien-3-one (dienogest), cyproterone acetate or chlormadinone acetate.

3. The pharmaceutical composition as claimed in claim 2, characterized in that the daily dose is 2 mg of dienogest or an equivalent amount of cyproterone acetate or chlormadinone acetate.

4. The pharmaceutical composition as claimed in claim 3, comprising daily dose units which are packed separately and can be removed singly and which are introduced into a pack unit for a period of at least 28, preferably 30 consecutive days, where the daily dose units comprise 2 mg of dienogest or an equivalent amount of cyproterone acetate or chlormadinone acetate together with one or more pharmaceutically acceptable excipients/carriers.

5. The pharmaceutical composition as claimed in claim 4 with a continuous administration of the dosage form for a period of at least 169 days or 25 weeks up to several years, preferably more than 2 years, for the prophylaxis and/or therapy of endometriosis without a negative influence on bone

metabolism and thus a reduction in bone density.

6. A kit comprising at least 28 daily dose units of a pharmaceutical composition as claimed in claim 1, 2 or 3.

7. The kit as claimed in claim 6, comprising 30 daily dose units of a pharmaceutical composition.

8. Use of progestogens having antiandrogenic activity, selected from the group of 17α-cyanomethyl-17-β-hydroxyestra-4,9-dien-3-one (dienogest), cyproterone acetate or chlormadinone acetate in a daily dose which does not exceed twice the ovulation-inhibitory dose, for manufacturing a pharmaceutical product for the prophylaxis and/or therapy of endometriosis without a negative influence on bone metabolism and thus a reduction in bone density.

9. The use of progestogens as claimed in claim 8, characterized in that the daily dose is 2 mg of dienogest or an equivalent amount of cyproterone acetate or chlormadinone acetate.

10. The use of progestogens as claimed in claim 8 or 9 for manufacturing a pharmaceutical product with continuous administration for a period of at least 169 days or 25 weeks up to several years, preferably more than 2 years, for the prophylaxis and/or therapy of endometriosis without a negative influence on bone metabolism and thus a reduction in bone density.

11. The use as claimed in claim 8, 9 or 10 comprising daily dose units which are packed separately and can be removed singly and which are introduced into a pack unit for a period of at least 28,

preferably 30 consecutive days, where the daily dose units comprise 2 mg of dienogest or an equivalent amount of cyproterone acetate or chlormadinone acetate together with one or more pharmaceutically acceptable excipients/carriers.

12. The use of progestogens as claimed in claim 8, 9, 10 or 11, characterized in that the pharmaceutical product is in the form of tablets, capsules, coated tablets, wafers, transdermal therapeutic systems, ampoules, suppositories, gels, ointments, implants, vaginal rings or nasal spray.