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PHARMACEUTICAL COMBINATION PREPARATION THAT CONSISTS OF LHRH-ANALOGUES AND ANTIESTROGENS FOR TREATING GYNECOLOGICAL DISORDERS

The invention relates to a pharmaceutical combination preparation that consists of LHRH-analogues and antiestrogens with tissue-selective estrogenic action, as well as its use for treating gynecological disorders, especially for treating endometriosis and myomas.

Gynecological disorders or diseases diminish to a considerable extent the quality of life of women and in this connection frequently lead, in addition to sometimes intolerable pain, to infertility. One of the most frequent diseases of women of child-bearing age (5% to 10%) is endometriosis. In association with this, severe pain during menstruation and low birthrate to sterility occur. Also myoma, a non-malignant tumor in the muscle tissue of the uterus, has a high incidence (in 10% to 25% of women around 30 years of age). Myomas can cause abnormally heavy menstrual bleeding (hypermenorrhea), menses that may be accompanied by pain (dysmenorrhea), or intermenstrual bleeding (metrorrhagia and menorrhagia) and can also, depending on the situation, lead to limited fertility. In addition to these types of dysmenorrhea that are caused by endometriosis and myomas, dysmenorrheas that are functionally induced (by hormonal and vegetative disorders) also occur.

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In the disease pictures that are described, gonal steroids (estrogens, gestagens), which are under the control of the hypothalamic-hypophyseal system, or growth factors (which also include cytokines) play a decisive role. These diseases or disorders are generally treated with hormones, such as LHRH-analogues (Lemay, A. et al., Fertil. Steril., 41, 863-871 (1984)). Some women experience side-effects with the latter, however. Thus, it is known that treatment with LHRH-agonists can lead to side-effects, such as, e.g., hypoestrogeneity (risk of osteoporosis) (Dawood, M. Y. et al, Fertil. Steril. 52, 21-25, (1989)), and danazol can result in androgenization symptoms (Dmowski, W. P. et al, Am. J. Obstet. Gynecol., 130, 41-48 (1978)).

To date, no established and validated long-term medicinal therapy exists for myomas. The current medicinal treatment is associated with considerable side-effects. Thus, the use of LHRH-agonists for more than six months results in a hypo-estrogenic state in women (Matta, W. H. et al, Br. Med. J., 294, 1523-1525, (1987)) and is associated with a reduction in bone density, which increases the risk of osteoporosis (Dawood, M. Y. Int. J. Gynecol. Obstet., 40, 29-42, (1993)). Other side-effects that are connected with estrogen deprivation (hot flashes) are also described by Dawood.

To avoid these side-effects, studies for treating gynecological disorders with LHRH-analogues and estrogens -- so-called Add-Back or HRT treatment schemes -- are known. It has not yet been possible, however, to find an estrogen dose that

completely prevents a reduction in bone density with LHRH-agonist therapy (Howell, R. et al., Fertil. Steril. 64, 474-481, (1995)), without simultaneously stimulating endometriosis or the endometrium, which can lead to endometrial hyperplasia and is associated with endometrial carcinomas.

The object of the invention is therefore to provide a pharmaceutical combination preparation for treating gynecological disorders, especially for treating endometriosis or myomas, with which a reduction in bone density is prevented and the drawbacks of previous hormone treatments are avoided.

The object is achieved according to the invention by a pharmaceutical combination preparation that comprises two active ingredients, of which the first active ingredient is an LHRH-analogue or a combination of LHRH-analogues, and the second active ingredient is an antiestrogen with tissue-selective estrogenic action.

The LHRH-analogue is an LHRH-agonist or LHRH-antagonist.

Within the meaning of the invention, all LHRH-antagonists and LHRH-agonists can be used. Preferred LHRH-analogues are selected from the group of compounds leuprorelin, cetrorelix, antide, buserelin, ramorelix, zoladex, 2-(4-acetyl-aminophenyl)-4,7-dihydro-7-(2-methoxybenzyl)-3-(N-methyl-N-benzylaminomethyl)-4-oxothieno-[2,3-b]-pyridine-5-carboxylic acid ethyl ester and 5-benzoyl-7-(2,6-difluorobenzyl)-4,7-dihydro-3-(N-methyl-N-benzylaminomethyl)-2-(4-propionylamidophenyl)-4-oxothieno [2,3-b]-pyridine.

The active ingredients generally come in separate forms of administration or even in a common form of administration in the case of orally bio-available LHRH-antagonists.

The LHRH-analogues that are preferably used are known and are described in Patents US 4,005,063 (leuprorelin), EP-B1 0 299 402 (cetrorelix), GB 1 523 623 (buserelin), EP-A 0 451 791 (ramorelix), WO-A 89/01944 (antide), WO-A 92/20711 (Ac-D-Nal-D-Cpa-D-Pal-Ser-Tyr-D-Cit-Leu-Lys(Mor)-D-Ala-NH_2), US 4,100,274 (zoladex) and WO-A 95/28405 2-(4-acetylaminophenyl)-4,7-dihydro-7-(2-methoxybenzyl)-3-(N-methyl-N-benzylaminomethyl)-4-oxothieno-[2,3-b]-pyridine-5-carboxylic acid ethyl ester.

They are produced and manufactured according to processes that are known in the art and, depending on the desired application, come in oral or nasal form, as an injection, or as a long-term preparation that is to be used topically or intravaginally. According to the invention, the LHRH-analogues can be administered as individual doses or as forms of deposits.

Depending on the form of administration, a dosage unit contains different amounts of active ingredient. Thus, with oral administration, 2 µg-20 mg of LHRH-analogues per kg of body weight is usually administered. Administration can be done in solid or liquid form. For intravenous, subcutaneous, intramuscular, intranasal, or intravaginal applications, the amounts of the LHRH-analogues are 0.02 µg-2.5 mg per kg of body weight. For parenteral application, preferably an isotonic common-salt or dextrose solution is used, which optionally is set

with a buffer to a pH of 5 to 9, preferably to the pH of the blood.

Leuprorelin is preferably used orally at a dosage of 2-100 µg/kg of body weight (daily dosage); a tablet preferably contains 0.1 to 5.0 mg of leuprorelin. The dose for parenteral use is preferably between 0.02 and 1.0 µg/kg of body weight.

Cetrorelix is preferably used in the form of a physiologic common-salt solution with a quantity of active ingredient of between 0.1-2.5 mg/kg of body weight. DE 43 42 092 also describes slow-release formulations of cetrorelix in DE 43 42 092.

Buserelin is preferably administered at the following dosages:

0.02-1 µg/kg of body weight (intravenous),

0.02-2 µg/kg of body weight (subcutaneous),

0.02-10 µg/kg of body weight (intramuscular),

0.1-50 µg/kg of body weight (intranasal) and

10-200 µg/kg of body weight (oral).

Also, as in the case of cetrorelix, slow-release formulations are possible. In the case of an implant, the latter contains 1-6 mg of cetrorelix.

Zoladex is preferably administered orally with a content of 50 µg-20 mg/kg of body weight and parenterally with a content of 0.2 µg-100 µg/kg of body weight or with a slow-release system (WO-A 93/24150).

Antide is administered like cetrorelix in an amount of 0.1-2.5 mg/kg of body weight.

The administration of ramorelix is preferably done in liposomal form.

Depot formulations for peptides (microparticles, implants) are described in, i.a., EP 0 505 966 and EP 0 315 875.

According to the invention, the second active ingredient component of the combination preparation is an antiestrogen with tissue-selective estrogenic action.

Antiestrogenic substances are used in, i.a., tumor therapy.

Antiestrogens with tissue-selective estrogenic action in terms of the invention are defined as so-called SERM's (selective estrogen receptor modulators), which exert their partially agonistic estrogenic action in a tissue- or organ-selective manner.

According to the invention, all antiestrogens with tissue-selective estrogenic action can be used. Preferably those used are selected from the group of raloxifene, droloxifene, centchroman, or derivatives thereof. Especially preferred are antiestrogens of the raloxifene type.

The above-mentioned antiestrogens are known. Thus, e.g., raloxifene is a 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]benzo[b]thiophene. In combination with parathyroid hormone, raloxifene and its derivatives are used to increase bone mass (EP 0 635 270).

The active-ingredient content of the antiestrogen that is used according to the invention is approximately 0.1 μg-10 mg of antiestrogen per kg of body weight with daily administration, depending on the form of administration. The antiestrogens can

be administered intravenously, subcutaneously, intramuscularly, orally, intranasally, or intravaginally. Slow-release formulations are also possible. The amount that is released daily is then also in the above-mentioned range.

The administration of the LHRH-analogue and the antiestrogen to patients can be done simultaneously and/or sequentially in time. Various treatment schemes are possible:

1. The LHRH-analogue is administered simultaneously with the tissue-selective antiestrogen over the same period. Administration can be done daily, every 3 days, weekly, or once a month over a period of 1 to 6 months. Extended use is also readily possible. In the case of monthly use, a depot formulation is preferred.

2. The LHRH-analogue is first administered simultaneously with the tissue-selective antiestrogen over a specific period. Relative to the time and frequency of administration (daily or at longer intervals), the indications given above under 1. hold true. Then, the treatment itself is continued with the antiestrogen.

For administration time and frequency, the indications that are given under 1. also hold true.

3. The treatment with the LHRH-analogue is carried out over a specific period and completed. The tissue-selective antiestrogen is administered thereafter. The time and frequency of use can be selected for each component, as indicated under 1.

It was noted that treatment with the combination preparation according to the invention, surprisingly enough, prevents the

previously observed LHRH-analogue-induced bone density reduction and does not re-stimulate endometriosis, which is inhibited in its growth, and also does not stimulate the growth of the normal endometrium in the uterus.

The pharmaceutical combination preparation according to the invention is especially suitable for long-term treatment of endometriosis or myomas and other steroid(sex)-hormone-dependent diseases since, on the one hand, the side-effects that normally occur under an LHRH-analogue (agonist or antagonist) treatment are avoided and, on the other hand, lost bone mass is again built up (e.g., when the tissue-selective antiestrogen is administered after an LHRH-analogue treatment is completed). At the same time, the growth inhibition of endometriosis is maintained, without the endometrium in the uterus being stimulated.

Variant 1 has turned out to be especially preferred for long-term therapy.

The pharmaceutical combination preparation according to the invention is produced, for example, by virtue of the fact that the LHRH-analogues and the antiestrogens with tissue-selective estrogenic action are formulated separately from one another with the commonly used pharmaceutical vehicles, adjuvants, and/or additives, whereby the forms of administration of the individual active ingredients do not have to be identical. It is eminently possible, e.g., for one active ingredient of the combination preparation to be administered orally, while the other active ingredient is administered subcutaneously or nasally.

In the case of orally bio-available LHRH-analogues, both active ingredients (LHRH-analogues plus antiestrogens) can also be formulated together for oral administration. Separate oral forms of administration are also possible.

The subject matter of the invention is also the packaging unit, which in the case of peptidergic LHRH-analogues comprises at least three components. It contains two physically separately manufactured active ingredients, of which one active ingredient is an LHRH-analogue or a combination of LHRH-analogues, and the other active ingredient is an antiestrogen with tissue-selective estrogenic action. The third component is directions on the application of the forms of administration, which is simultaneous and/or sequential in time.

Another subject matter of the invention is the use of an LHRH-analogue or a combination of LHRH-analogues and an antiestrogen with tissue-selective estrogenic action for treating gynecological disorders, especially for treating endometriosis and myomas.

Below, the invention is to be explained in more detail by the examples without, however, being limited to said examples.

Embodiments

Example 1

Influence of LHRH-Administration and Raloxifene Administration on Experimentally Induced Endometriosis in Rats

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1.1 Comparison of the Administration in Each Case of an Active Ingredient Component by Itself with the Simultaneous Administration of Active Ingredients (Combination Preparation)

Method:

Endometrium pieces were transplanted into various areas of the abdominal cavities of 60 animals.

Four weeks later, the development of endometriosis (cystic endometriosis foci) was checked.

The animals were then treated over 4 weeks with the LHRH-antagonists antide (0.5 mg/animal every 3 days s.c.) and raloxifene (3 mg/animal per day p.o.) in each case alone or in a combination of the two compounds. At the end, the size of the endometriosis focus before the start of treatment was compared with the values after 4 weeks of treatment.

The combination of LHRH-antagonist plus raloxifene resulted in complete regression of endometriosis without a significant reduction in bone mass. At the same time, no estrogenic effects on the uterus (no stimulation of the endometrium) were shown.

By comparison, treatment with the LHRH-antagonist by itself led to complete regression of the endometriosis focus, but at the same time also to a drop in the endogenic estrogen levels, which

correspond to an ovariectomy. It resulted in a clear reduction of bone density or an increase in the osteoclast activity.

Administration of raloxifene resulted in only partial regression of endometriosis.

1.2 LHRH-Antagonist Antide and Raloxifen for Administration That Is Simultaneous and Sequential in Time

For the first 2 weeks, 60 animals received the LHRH-antagonist antide and raloxifene in parallel, and for the following 2 weeks they received raloxifene alone. The dosages were selected as under 1.1.

As a result, as with the simultaneous administration of the active ingredients, complete regression of the endometriosis was also noted without a significant reduction in bone mass. At the same time, no estrogenic effects on the uterus were shown.

1.3 Administration of the Combination Preparation That Is Sequential in Time

Over 2 weeks, 60 animals received the LHRH-antagonist antide. After LHRH administration was completed, raloxifene was then administered for 2 weeks.

This sequential treatment also resulted in 100% regression of the endometriosis without a reduction in bone density.

Example 2

Analogously to Example 1, treatment with LHRH-antagonist Ac-D-Nal-D-Cpa-D-Pal-Ser-Tyr-D-Cit-Leu-Lys(Mor)-D-Ala-NH_2 and droloxifene was carried out on 40 animals.

The same results were achieved as under Example 1.

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Claims

1. Pharmaceutical combination preparation that contains two active ingredients, whereby one active ingredient is an LHRH-analogue or a combination of LHRH-analogues, and the other active ingredient is an antiestrogen with tissue-selective estrogenic action.

2. Combination preparation according to claim 1, characterized in that the LHRH-analogue is an LHRH-agonist or an LHRH-antagonist.

3. Combination preparation according to claim 1 or 2, wherein the LHRH-analogue is selected from the group of compounds leuprorelin, cetrorelix, buserelin, antide, Ac-D-Nal-D-Cpa-D-Pal-Ser-Tyr-D-Cit-Leu-Lys(Mor)-D-Ala-NH_2, ramorelix, zoladex, or derivatives thereof.

4. Combination preparation according to one of claims 1 to 3, wherein the LHRH-analogue or the combination of the LHRH-analogues is/are orally bio-available.

5. Combination preparation according to one of claims 1 to 4, wherein the LHRH-analogue is a non-peptidergic LHRH-agonist or LHRH-antagonist.

6. Combination preparation according to one of claims 1 to 5, wherein the antiestrogen is selected from the group of compounds raloxifene, droloxifene, centchroman or derivatives thereof.

7. Combination preparation according to one of claims 1 to 6, wherein the antiestrogen is of the raloxifene type.

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8. Combination preparation according to one of claims 1 to 7, wherein the two active ingredients are present in separate forms of administration.

9. Combination preparation according to one of claims 1 to 7, wherein the two active ingredients are present in common forms of administration.

10. Process for the production of a pharmaceutical combination preparation, wherein an LHRH-analogue or a combination of LHRH-analogues and an antiestrogen with tissue-selective action are formulated together or separately with commonly used pharmaceutical vehicles, adjuvants and/or additives.

11. Process according to claim 10, wherein the LHRH-analogue or the combination of LHRH-analogues and the antiestrogen with tissue-selective estrogenic action are formulated separately from one another.

12. Process according to claim 10, wherein the LHRH-analogues or the combination of LHRH-analogues and the antiestrogen with tissue-selective estrogenic action are formulated together.

13. Use of an LHRH-analogue or a combination of LHRH-analogues and an antiestrogen with tissue-selective estrogenic action for treating gynecological disorders, especially for treating endometriosis and myomas.

14. Use according to claim 13, wherein LHRH-analogues and antiestrogens are used simultaneously and/or sequentially in time.

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15. Packaging unit that contains two physically separately manufactured active ingredients, of which one active ingredient is an LHRH-analogue or a combination of LHRH-analogues and the other active ingredient is an antiestrogen with tissue-selective estrogenic action and that contains as a third component instructions on the application of the forms of administration that are simultaneous and/or sequential in time.