(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
29 March 2001 (29.03.2001)

PCT

(10) International Publication Number
WO 01/21194 A2

(51) International Patent Classification[7]: A61K 38/09

(21) International Application Number: PCT/EP00/09212

(22) International Filing Date:
20 September 2000 (20.09.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/155,478 23 September 1999 (23.09.1999) US

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(81) Designated States *(national)*: AU, BG, BR, BY, CA, CN, CZ, DZ, EE, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LT, LV, MK, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, UA, US, UZ, YU, ZA.

(84) Designated States *(regional)*: Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published:
— *Without international search report and to be republished upon receipt of that report.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/21194 A2

(54) Title: METHOD FOR THE THERAPEUTIC MANAGEMENT OF EXTRAUTERINE PROLIFERATION OF ENDOMETRIAL TISSUE, CHRONIC PELVIC PAIN AND FALLOPIAN TUBE OBSTRUCTION

(57) Abstract: The present invention provides a method for therapeutic management of extrauterine proliferation of endometrial tissue, chronic pelvic pain and fallopian tube obstruction by short term induction treatment with an LH-RH antagonist for 4 to 12 weeks. According to another aspect of the present invention, the short term LH-RH treatment is followed by the combined or separate administration of one or more active agents selected from the group consisting of a contraceptive, preferably an oral contraceptive, a non-steroidal anti-rheumatic agent, an analgetic, an androgen other than a 17-alpha-alkyl substituted testosterone or any combinations thereof. According to a further aspect of the present invention a pharmaceutical composition comprising an LHRH antagonist and one or more active agents selected from the group consisting of a contraceptive, preferably an oral contraceptive, a non-steroidal anti-rheumatic agent, an analgetic, an androgen other than a 17-alpha-alkyl substituted testosterone or any combinations thereof are provided.

Method for the therapeutic management of extrauterine proliferation of endometrial tissue, chronic pelvic pain and fallopian tube obstruction

Field of Invention

Endometriosis is one of the most frequently encountered pathologies diagnosed amongst gynecological patients. For example, between 10% and 25% of women presenting with gynecological symptoms in UK and in the USA are affected. Clinical diagnosis is made usually by laparoscopic observation of hemorrhagic or fibrotic foci on the pelvic organs. The ectopic endometrial tissue responds to ovarian hormones undergoing cyclic changes. The cyclical bleeding from the endometric deposit contributes to a local inflammatory reaction. Endometriosis commonly affects women during their childbearing years with an incidence of at least 1% (see Shaw, R.W. (1993), An Atlas of Endometriosis. The Parthenon Publishing Group).

Endometriosis is usually classified into endometriosis (genitalis) interna (adenomyosis), endometriosis genitalis externa and endometriosis extragenitalis.

Chronic pelvic pain may occur either in relation to endometriosis or as an independent disease.

Fallopian tube obstruction (FTO) is a relatively common disease and may account to for up to 20 % of cases of tubal infertility (see Winfield, A.C. et al., Apparent cornual occlusion in hysterosalpingography: Reversal by glucagon. AJR Am J Roentgenol 1982; 139: 525 – 527).

Background information and Prior Art

Sampson suggested that menstrual regurgitation and subsequent implantation of endometrial tissue on the peritoneal face results in endometriosis [Sampson, J.A.

(1927), Peritoneal endometriosis due to menstrual dissemination of the endometrial tissue into the peritoneal cavitiy. Am. J. Obstet. Gynecol., 14, 422.]
Several aetiologic factors may be involved in the pathogenesis of endometriosis :

Dmowski et. al. suggested that genetic and immunological factors lead to endometriosis [Dmowski, W.P., Steele, R.W. and Baker, G.F. (1981). Deficient cellular immunity in endometriosis. Am. J. Obstet. Gynecol., 141, 377]
Vascular and lymphatic embolization to distant sites has been demonstrated and explains the (rare) finding of endometriosis outside the peritoneal cavity, e.g. skin, lung, kidney.
Cells lining the Müllerian duct arise from primitive cells which differentiate into peritoneal cells and the cells on the surface of the ovaries. It is proposed that these adult cells undergo de-differentiation back to their primitive origin and then transform into endometrial cells [Levander, G. (1941), Bone formation by induction. An *experimental study. Arch. Klin. Chir., 202, 497]*
Dysmenorrhea, acute or chronic pelvic pain, dyspareunia, and infertility perform the most frequent clinical symptoms reported.

FTO represents a heterogenous group of underlying pathology, preliminary intrinsic occlusion or extrinsic compression from estrogen–sensitive disorders, such as endometriosis, adenomyosis, endosalpingiosis, and myomata. FTO is frequently diagnosed by hysterosalpingography, besides laparascopy.

First choice of treatment comprises laparoscopic removal of endometric lesions. This procedure may be followed by the treatment with Danazol or LHRH agonist (for a period of six months). Women being treated with Danazol might experience gastrointestinal and hepatic disorders as well as severe androgenic side effects.

It was also proposed from a theoretical viewpoint for treatment of endometriosis and uterine myoma to use the immediate suppression by administration of a LHRH antagonist to reducing the duration of treatment and faster improvement of subjective symtoms [Th. Reissmann et al. Human Reproduction vol. 10 No. 8 pp.1974-1981,(1995)]

Further Hodgen teaches in the US Patent 5,658,884 a regime for therapeutic management of a gonadal dependent condition by reducing the estrogen supply by means of long-term administration of an GnRH antagonist for 6 months or longer in an amount effective to inhibit proliferation of endometrial tissue without substantially stopping the production of endogenous estrogen. For this purpose, Hodgen teaches such a regimen or dose of GnRH antagonist to achieve a 24 hour serum estradiol level in the range of about 25 to 50 and preferably about 35 to 45 pg/ml. However, Hodgen does not describe estradiol serum levels oscillating between 50 pg/ml and 75 pg/ml. Moreover, Hodgen only teaches in the US Patent 5,658,884 a continuous long-term treatment (on a daily or periodic basis, the latter meaning a weekly or monthly administration) but not a short-term induction treatment for only 4 to 12 weeks. Hodgen also does not describe any combination therapy comprising the GnRH antagonist in the treatment of endometrosis. The treatment is only described on monkeys and also includes the performance of a costly and repeated progesterone challenge test to provide an 24 hour average serum estradiol level of 30 to 50 pg/ml.

As a consequence of the flare-up effect of LHRH-agonistic therapy an exacerbation of symptoms might occur during some days. Following prolonged treatment which is required to avoid the re-proliferation of endometric tissue hormonal withdrawal symptoms as well as demineralization of bones occur.

Therefore, effective drug therapy should immediately reduce the residual extrauterine endometrial tissue present after laparoscopic surgery. Duration of therapy should be only 4 to 12 weeks without the occurrence of any major hormonal withdrawal symptoms or ovarian cyst formation.

LHRH antagonists exert an immediate onset of hormonal suppression, and therefore benign gynecological tumors, such as uterine fibroids decrease within short time [Human Reproduction 1998, 13]

Object of the Invention

The present invention relates to the improvement of the medical treatment of extrauterine proliferation of endometrial tissue, i. e. the administration of LHRH antagonists in patients with clinical symptoms of endometriosis, the improvement consisting of :

immediate reduction of ectopic endometrial tissue

immediate cessation of symptoms, e.g. severe pain, chronic pelvic pain and dysmenorrhea

prevention of any progress of the disease

avoidance of hormonal withdrawal symptoms

prevention of ovarian cyst formation, demineralization of bones as well as of gastrointestinal or hepatic disorders.

The inventive medical therapy can start in the early to mid follicular phase, preferably on cycle day one to three. During the treatment the estradiol serum concentration levels are kept between 35 pg/ml and 80 pg/ml, preferably between about 45-75 pg/ml, more preferably between about 50-75 pg/ml. The LHRH antagonist is administered only for 4 to 12 weeks (short-term induction treatment), either by daily, weekly or monthly administration. Following the short-term induction treatment, the administration of a contraceptive, a non-steroidal anti-rheumatic, an analgetic, an androgen other than 17-alpha-alkyl substituted testosterone or any combinations thereof is provided according to the present invention.

Summary of the Invention

In the treatment of extrauterine endometrial tissue with an LHRH antagonist, therapy is started on menstrual cycle day one to three. Before starting LHRH-antagonist therapy the diagnosis is performed by laparoscopy.

In cases of severe pain, LHRH antagonist therapy might be initiated without prior laparascopy.

Therapy will continue until clinical symptomatology has resolved and no proliferation of the endometrium is seen. Due to the immediate onset of suppression of the gonadotropins LH and FSH as well of sex steroids estradiol and progesterone no

further proliferation of the endometrium occurs. Benign tumors or other sex steroid dependent lesions, like endometriosis decrease within four to twelve weeks of therapy. Due to the lack of flare-up no ovarian cysts develop.

Furthermore, no hormonal withdrawal symptoms are seen as the estradiol values are kept in the range of the early follicular phase of 35 to 80 pg/ml, preferably between about 45-75 pg/ml, more preferably between about 50-75 pg/ml without further increase or decrease. No titering of the dosage of the LHRH antagonist , e.g. by conducting a costly progesterone challenge test, is necessary.

The method of therapeutic management of extrauterine proliferation of endometrial tissue the improvement according to the invention therefore embraces:
immediate reduction of ectopic endometrial tissue
prevention of any progress of the disease
avoidance of hormonal withdrawal symptoms
prevention of ovarian cyst formation, demineralization of bones as well as of gastrointestinal or hepatic disorders
start of medical therapy on cycle day one to three and maintenance of estradiol levels at values of the early follicular phase throughout the entire duration of treatment by means of administration of a LHRH antagonist wherein the antagonist is preferabely cetrorelix, teverelix, ganirelix, antide or abarelix. The antagonist can also be the LHRH antagonist D-63153 (Ac-D-Nal-D-pCl-Phe-D-Pal-Ser-N-Me-Tyr-D-Hci-Nle-Arg-Pro-D-Ala-NH2) as described in the German Patent Application No. 199 11 771.3 filed on March 11, 1999.

The LHRH antagonist may be given for 4 to 12 weeks in a weekly dose of 3 to 10 mg per week or for 4 to 12 weeks in a daily dose of 0.25 mg to 0.5 mg/day.

It is also possible to give the LHRH antagonist 4 to 12 weeks in a monthly dose of 12 to 40 mg per month.

In a repeat therapeutic treatment the LHRH antagonist is given for 4 to 12 weeks and the treatment is repeated two or three times a year, whereby a repeated

treatment does not following directly after a short-term induction treatment. Usually a period of time of weeks or months, where no LHRH antagonist is administered, is between the end of the short-term induction treatment and the start of the repeat treatment.

To demonstrate the feasibility to maintain a low estradiol secretion under adjusted LHRH- antagonist treatment so that a therapeutic suppression occurs without withdrawal symtoms nine patients with confirmed endometriosis were treated with 3 mg of Cetrorelix acetate s.c. by weekly administration for 8 weeks. While patients compliance was excellent avoiding any hot flushes or other withdrawal symptoms and without any progress of the disease confimed by 2 nd look laparascopy the mean estradiol serum concentrations oscillated between 37 pg/ml and 64 pg/ml, preferably between 45-75 pg/ml, more preferably between about 50-75 pg/ml. Histological biopsies showed no proliferation of the endometrium at the end of treatment. No ovarian cyst formation occurred.

The figure 1 shows the continuous estradiol suppression to values of the early follicular phase (range of 35 pg/ml to 80 pg/ml, preferably between 45-75 pg/ml, more preferably between about 50-75 pg/ml) obtained in patients with endometriosis by a weekly dose of 3 mg of Cetrorelix (LHRH antagonist) for 8 weeks. Immediate and continuous suppression of estradiol levels is obtained without any signs of estradiol withdrawal symptoms and without proliferation of the endometrium at the end of treatment.

Fig. 2 shows estradiol serum levels after administration of cetrorelix at a weekly dose of 1 mg resp. 3 mg once per week. The estradiol serum levels are between about 35-80 pg/ml, preferably between about 45-75 pg/ml, more preferably between about 50-75 pg/ml.

The endometriosis patient with distinctive symptomatic pain is suffering from a chronic disease. Surgical methods in sense of curative therapy as well as medicinal treatment to suppress the sexual steroid secretion of the patient often result only in a

temporary improvement. The relapse rate of the discomforts is very high and about 70% within 5 years after finishing therapy (Schweppe, 1999).

At the same time the radical surgical therapy and the suppression of the estrogen secretion leads to considerable side effects. The radical surgical therapy in sense of hysterectomy with bilateral adnexectomy is no adequate therapy for the younger, premenopausal woman. The chronical lack of estrogen leads to the following vegetative symptoms: hot flashes, sweating, dryness of the vagina, depressive feelings and also holds the risk of osteoporosis. The alternative therapy with the synthetic steroidal compound Danazol may cause virilizing symptoms because of the androgenic effect.

Aim of the medicinal therapy of patients with endometriosis with symptomatic pain is to obtain a treatment without side effects, especially avoiding the negative effects of estrogen suppression and which is long-lasting after finishing therapy. The specific pharmacological mode of action of LHRH antagonists allows new possibilities for treatment of endometriosis.

The weekly administration of an adequate dose of an LHRH antagonist, e.g. 3 mg Cetrotide® s.c./ per week over a period of eight weeks leads to a controlled suppression of estrogen secretion so that serum concentrations between about 35 pg/ml and about 80 pg/ml, preferably between about 45-75 pg/ml, more preferably between about 50-75 pg/ml are obtained. In this serum concentration range no vegetative symptoms arise. Also the development of osteoporosis can be avoided. The symptomatic pain will be effectively suppressed in all stages of the disease (rAFS I – IV). In the stages rAFS I – II a clinical regression of the disease in sense of decrease of the implantation area is noticed (Felberbaum et. al., 2000).

In a preferred embodiment of this invention, after this treatment period of eight to twelve weeks the patient could take a contraceptive, preferably an oral contraceptive, preferably with gestagen components, unless there is a wish for pregnancy. In this connection combinations with Lynestronol 2 mg with 0,04 mg

Ethinylestradiol or 2,5 mg Lynestrenol with 0,05 mg of Ethinylestradiol (e.g. Yermonil®, Lyn-ratiopharm-Sequenz®) have to be mentioned.

A combination therapy with androgens other than 17-alpha-alkyl substituted testosterones such as danazol may also be applied subsequently to the short-term induction regimen with the LHRH antagonist either alone or in combination with non-steroidal anti-rheumatics and/or analgetics. An example for a suitable androgene is halotestin™ (fluoximesterone).

The treatment with a contraceptive, preferably an oral contraceptive, preferably containing gestagens, should be individually continued until typical pain sensation occurs. In this stage the patient will have relatively small menstrual bleeding as an effect of the gestagen component of this contraceptive, preferably oral contraceptive. For covering also the especially critical pre-menstrual and menstrual days with regard to pain sensation in this phase a concomitant medication with appropriate non-steroidal anti-rheumatic drugs, e.g. diclophenac, ibuprofen, indometeacin, oxicam derivates or acetylsalicylic acid may be given. Also an analgetic such as flupirtinmaleat (Katadolon®) can be administered.

If further pain symptoms occur during this combination therapy with gestagenic contraceptives, preferably oral contraceptives, a daily, weekly or monthly therapy with the adequate dose of an LHRH antagonist as described above may be repeated. Detailed information on the respective treatment options are given below. If the patient is absolutely free of pain treatment can be changed to gestagenic contraceptive, preferably oral contraceptive,s in combination with concomitant medication of appropriate non-steroid anti-rheumatic drugs or analgetics.

This therapy using the intermittent administration of an LHRH antagonist leads to a new and innovative unlimited treatment without side effects and lowers treatment burden for the patient significantly.

Pharmaceutical Formulations Suitable for Treatment

Pharmaceutical formulations of the LHRH antagonist suitable for the therapeutic management of extrauterine proliferation of endometrial tissue, chronic pelvic pain and fallopian tube obstruction may be for example

a) acetate salt formulations in the concentration of 1 mg/1 ml or lower where the powder may be dissolved in Water for Injection (Wfl) or in Gluconic Acid (GA);

b) acetate salt formulations in the concentration of 1.5 mg/1 ml to 5.0 mg /1 ml, preferably 2.5 mg/1 ml where the powder may be dissolved in Water for Injection (Wfl) or in Gluconic Acid (GA);

c) pamoate salt formulations in the concentration of 10 mg/1 ml to 30 mg/1 ml, preferably 15 mg/1 ml where the lyophylisate powder may be dissolved in Gluconic Acid (GA) or in Water for Injection (Wfl.

According to one aspect of the present invention in the method of therapeutic management of extrauterine proliferation of endometrial tissue, chronic pelvic pain and/or fallopian tube obstruction (FTO), the improvement consisting of administration of an LHRH antagonist in the form of a short-term induction treatment for a period of about 4 to 12 weeks to a patient in need of such treatment, whereby subsequently the administration of the LHRH antagonist is ceased, is provided.

The duration of the short term induction treatment is about 4 to about 12 weeks, that means that the treatment can be between about 28 to about 84 days or from about one to about three months.

According to another aspect of the present invention in a method as mentioned above the improvement is provided, wherein the LHRH antagonist is administered such that the estrogen serum concentration level is between about 35 pg/ml and

about 80 pg/ml, preferably between about 45–75 pg/ml, more preferably about 50-75 pg/ml.

According to another aspect of the present invention in a method as mentioned above the improvement is provided, characterized in that the short-term induction treatment with the LHRH antagonist is followed by administration of a contraceptive, preferably an oral contraceptive.

According to another aspect of the present invention in a method as mentioned above the improvement is provided, characterized in that the short-term induction treatment with the LHRH antagonist is followed by administration of a non-steroidal anti-rheumatic agent.

According to another aspect of the present invention in a method as mentioned above the improvement is provided, characterized in that the short-term induction treatment with the LHRH antagonist is followed by administration of an analgetic.

According to another aspect of the present invention in a method as mentioned above the improvement is provided, characterized in that the short-term induction treatment with the LHRH antagonist is followed by administration of an androgen other than a 17-alpha-alkyl substituted testosterone.

According to another aspect of the present invention in a method as mentioned above the improvement is provided, characterized in that the short-term induction treatment with the LHRH antagonist is followed by the combined or separate administration of one or more active agents selected from the group consisting of a contraceptive, preferably an oral contraceptive, a non-steroidal anti-rheumatic agent, an analgetic, an androgen other than a 17-alpha-alkyl substituted testosterone or any combinations thereof.

According to another aspect of the present invention in a method as mentioned above the improvement is provided, characterized in that the LHRH antagonist is

administered starting in the early to mid follicular phase, preferably on cycle day one to three.

According to another aspect of the present invention in a method as mentioned above the improvement is provided, characterized in that the LHRH antagonist is selected from the group consisting of cetrorelix, teverelix, ganirelix, antide, abarelix and D-63153.

According to another aspect of the present invention in a method as mentioned above the improvement is provided, characterized in that the LHRH antagonist is administered during the short-term induction treatment for 4 to 12 weeks at a weekly dose of 3 to 10 mg per week.

According to another aspect of the present invention in a method as mentioned above the improvement is provided, characterized in that the LHRH antagonist is administered during the short-term induction treatment for 4 to 12 weeks at a daily dose of 0.25 mg to 0.5 mg/day.

According to another aspect of the present invention in a method as mentioned above the improvement is provided, characterized in that the LHRH antagonist is administered during the short-term induction treatment for 4 to 12 weeks at a monthly dose of 12 to 40 mg per month.

According to another aspect of the present invention in a method as mentioned above the improvement is provided, characterized in that the LHRH antagonist is given for the induction treatment during 4 to 12 weeks and the treatment is repeated two or three times a year.

According to a further aspect of the present invention a pharmaceutical composition for treating extrauterine proliferation of endometrial tissue, chronic pelvic pain and/or fallopian tube obstruction (FTO) comprising an LHRH antagonist and optionally one or more agents selected from the group consisting of a contraceptive, preferably an oral contraceptive, a non-steroidal anti-rheumatic agent, an analgetic agent, an

androgen agent other than a 17-alpha-alkyl substituted testosterone or any combinations thereof, optionally together with pharmaceutically acceptable excipients, whereby the LH-RH antagonist is administered to a patient in need thereof in a short term induction treatment for a period of about 4 to 12 weeks, then the administration of the LH-RH antagonist is ceased and optionally the one or more agents selected from the group consisting of a contraceptive, preferably an oral contraceptive, a non-steroidal anti-rheumatic agent, an analgetic, an androgen other than a 17-alpha-alkyl substituted testosterone or any combinations thereof, are administered together or separately to the patient is provided.

Suitable excipients and dosage forms are for example described by K.H. Bauer, K.-H. Frömming and C. Führer, Lehrbuch der Pharmazeutischen Technologie, 6th edition, Stuttgart 1999, pages 163-186 (excipients) and pages 227-386 (dosage forms), including the references as cited therein.

The LH-RH antagonist can be administered for example sucutaneous (s.c.), intramuscular (i.m.) or inhalative. The agents selected from the group consisting of a contraceptive, preferably an oral contraceptive, a non-steroidal anti-rheumatic agent, an analgetic, an androgen other than a 17-alpha-alkyl substituted testosterone or any combinations thereof can be administered as known in the art (see for example the German, European or U.S. pharmacopoeia), preferably oral or inhalative.

According to another aspect of the present invention, a pharmaceutical composition as mentioned above is provided wherein the LHRH antagonist is administered such that the estrogen serum concentration level is between about 35 pg/ml and about 80 pg/ml, preferably between about 45–75 pg/ml, more preferably about 50-75 pg/ml.

According to another aspect of the present invention, a pharmaceutical composition as mentioned above is provided wherein the short-term induction treatment with the LHRH antagonist is followed by administration of a contraceptive, preferably an oral contraceptive.

According to another aspect of the present invention, a pharmaceutical composition as mentioned above is provided wherein the short-term induction treatment with the LHRH antagonist is followed by administration of a non-steroidal anti-rheumatic agent.

According to another aspect of the present invention, a pharmaceutical composition as mentioned above is provided wherein the short-term induction treatment with the LHRH antagonist is followed by administration of an analgetic.

According to another aspect of the present invention, a pharmaceutical composition as mentioned above is provided wherein the short-term induction treatment with the LHRH antagonist is followed by administration of an androgen other than a 17-alpha-alkyl substituted testosterone.

According to another aspect of the present invention, a pharmaceutical composition as mentioned above is provided wherein the short-term induction treatment with the LHRH antagonist is followed by the combined or separate administration of one or more active agents selected from the group consisting of a contraceptive, preferably an oral contraceptive, a non-steroidal anti-rheumatic agent, an analgetic, an androgen other than a 17-alpha-alkyl substituted testosterone or any combinations thereof.

According to another aspect of the present invention, a pharmaceutical composition as mentioned above is provided wherein the LHRH antagonist is administered starting in the early to mid follicular phase, preferably on cycle day one to three.

According to another aspect of the present invention, a pharmaceutical composition as mentioned above is provided wherein the LHRH antagonist is selected from the group consisting of cetrorelix, teverelix, ganirelix, antide, abarelix and D-63153.

According to another aspect of the present invention, a pharmaceutical composition as mentioned above is provided wherein the LHRH antagonist is administered during

the short-term induction treatment for 4 to 12 weeks at a weekly dose of 3 to 10 mg per week.

According to another aspect of the present invention, a pharmaceutical composition as mentioned above is provided wherein the LHRH antagonist is administered during the short-term induction treatment for 4 to 12 weeks at a daily dose of 0.25 mg to 0.5 mg/day.

According to another aspect of the present invention, a pharmaceutical composition as mentioned above is provided wherein the LHRH antagonist is administered during the short-term induction treatment for 4 to 12 weeks at a monthly dose of 12 to 40 mg per month.

According to another aspect of the present invention, a pharmaceutical composition as mentioned above is provided wherein the LHRH antagonist is given for the induction treatment during 4 to 12 weeks and the treatment is repeated two or three times a year.

According to another aspect of the present invention, a pharmaceutical composition as mentioned above is provided, wherein the the one or more active agents selected from the group consisting of a contraceptive, preferably an oral contraceptive, a non-steroidal anti-rheumatic agent, an analgetic, an androgen other than a 17-alpha-alkyl substituted testosterone or any combinations thereof, are in the same or separate dosage forms.

According to another aspect of the present invention, a use of an LH-RH antagonist for the preparation of a medicament for the therapeutic management of extrauterine proliferation of endometrial tissue, chronic pelvic pain and/or fallopian tube obstruction (FTO), whereby the LHRH antagonist is administered in the form of a short-term induction treatment for a period of about 4 to 12 weeks to a patient in need of such treatment and then the administration of the LHRH antagonist is ceased, is provided.

According to another aspect of the present invention, a use of an LH-RH antagonist as mentioned above is provided wherein the LHRH antagonist is administered such that the estrogen serum concentration level is between about 35 pg/ml and about 80 pg/ml, preferably between about 45–75 pg/ml, more preferably about 50-75 pg/ml.

According to another aspect of the present invention, a use of an LH-RH antagonist as mentioned above is provided, wherein the short-term induction treatment with the LHRH antagonist is followed by administration of a contraceptive, preferably an oral contraceptive.

According to another aspect of the present invention, a use of an LH-RH antagonist as mentioned above is provided, wherein the short-term induction treatment with the LHRH antagonist is followed by administration of a non-steroidal anti-rheumatic agent.

According to another aspect of the present invention, a use of an LH-RH antagonist as mentioned above is provided, wherein the short-term induction treatment with the LHRH antagonist is followed by administration of an analgetic.

According to another aspect of the present invention, a use of an LH-RH antagonist as mentioned above is provided, wherein the short-term induction treatment with the LHRH antagonist is followed by administration of an androgen other than a 17-alpha-alkyl substituted testosterone.

According to another aspect of the present invention, a use of an LH-RH antagonist as mentioned above is provided, wherein the short-term induction treatment with the LHRH antagonist is followed by the combined or separate administration of one or more active agents selected from the group consisting of a contraceptive, preferably an oral contraceptive,, a non-steroidal anti-rheumatic agent, an analgetic, an androgen other than a 17-alpha-alkyl substituted testosterone or any combinations thereof.

According to another aspect of the present invention, a use of an LH-RH antagonist as mentioned above is provided, wherein the LHRH antagonist is administered starting in the early to mid follicular phase, preferably on cycle day one to three.

According to another aspect of the present invention, a use of an LH-RH antagonist as mentioned above is provided, wherein the LHRH antagonist is selected from the group consisting of cetrorelix, teverelix, ganirelix, antide, abarelix and D-63153.

According to another aspect of the present invention, a use of an LH-RH antagonist as mentioned above is provided, wherein the LHRH antagonist is administered during the short-term induction treatment for 4 to 12 weeks at a weekly dose of 3 to 10 mg per week.

According to another aspect of the present invention, a use of an LH-RH antagonist as mentioned above is provided, wherein the LHRH antagonist is administered during the short-term induction treatment for 4 to 12 weeks at a daily dose of 0.25 mg to 0.5 mg/day.

According to another aspect of the present invention, a use of an LH-RH antagonist as mentioned above is provided, wherein the LHRH antagonist is administered during the short-term induction treatment for 4 to 12 weeks at a monthly dose of 12 to 40 mg per month.

According to another aspect of the present invention, a use of an LH-RH antagonist as mentioned above is provided, wherein the LHRH antagonist is given for the induction treatment during 4 to 12 weeks and the treatment is repeated two or three times a year.

According to another aspect of the present invention, a use of an LH-RH antagonist and one or more active agents selected from the group consisting of a contraceptive, preferably an oral contraceptive, a non-steroidal anti-rheumatic agent, an analgetic, an androgen other than a 17-alpha-alkyl substituted testosterone, or any combinations thereof, for the preparation of a medicament for the therapeutic

management of extrauterine proliferation of endometrial tissue, chronic pelvic pain and/or fallopian tube obstruction (FTO), whereby the LHRH antagonist is administered in the form of a short-term induction treatment for a period of about 4 to 12 weeks to a patient in need of such treatment, then the administration of the LHRH antagonist is ceased and the one or more active agent selected from the group consisting of a contraceptive, preferably an oral contraceptive, a non-steroidal anti-rheumatic agent, an analgetic, an androgen other than a 17-alpha-alkyl substituted testosterone, or any combinations thereof, are administered together or separately to the patient, is provided.

According to another aspect of the present invention the use of an LH-RH antagonist and one or more active agents as mentioned above is provided, wherein the LHRH antagonist is administered such that the estrogen serum concentration level is between about 35 pg/ml and about 80 pg/ml, preferably between about 45–75 pg/ml, more preferably about 50-75 pg/ml.

According to another aspect of the present invention the use of an LH-RH antagonist and one or more active agents as mentioned above is provided, wherein the short-term induction treatment with the LHRH antagonist is followed by administration of a contraceptive, preferably an oral contraceptive.

According to another aspect of the present invention the use of an LH-RH antagonist and one or more active agents as mentioned above is provided, wherein the short-term induction treatment with the LHRH antagonist is followed by administration of a non-steroidal anti-rheumatic agent.

According to another aspect of the present invention the use of an LH-RH antagonist and one or more active agents as mentioned above is provided, wherein the short-term induction treatment with the LHRH antagonist is followed by administration of an analgetic.

According to another aspect of the present invention the use of an LH-RH antagonist and one or more active agents as mentioned above is provided, wherein the short-

term induction treatment with the LHRH antagonist is followed by administration of an androgen other than a 17-alpha-alkyl substituted testosterone.

According to another aspect of the present invention the use of an LH-RH antagonist and one or more active agents as mentioned above is provided, wherein the short-term induction treatment with the LHRH antagonist is followed by the combined or separate administration of one or more active agents selected from the group consisting of a contraceptive, preferably an oral contraceptive, a non-steroidal anti-rheumatic agent, an analgetic, an androgen other than a 17-alpha-alkyl substituted testosterone or any combinations thereof.

According to another aspect of the present invention the use of an LH-RH antagonist and one or more active agents as mentioned above is provided, wherein the LHRH antagonist is administered starting in the early to mid follicular phase, preferably on cycle day one to three.

According to another aspect of the present invention the use of an LH-RH antagonist and one or more active agents as mentioned above is provided, wherein the LHRH antagonist is selected from the group consisting of cetrorelix, teverelix, ganirelix, antide, abarelix and D-63153.

According to another aspect of the present invention the use of an LH-RH antagonist and one or more active agents as mentioned above is provided, wherein the LHRH antagonist is administered during the short-term induction treatment for 4 to 12 weeks at a weekly dose of 3 to 10 mg per week.

According to another aspect of the present invention the use of an LH-RH antagonist and one or more active agents as mentioned above is provided, wherein the LHRH antagonist is administered during the short-term induction treatment for 4 to 12 weeks at a daily dose of 0.25 mg to 0.5 mg/day.

According to another aspect of the present invention the use of an LH-RH antagonist and one or more active agents as mentioned above is provided, wherein the LHRH

antagonist is administered during the short-term induction treatment for 4 to 12 weeks at a monthly dose of 12 to 40 mg per month.

According to another aspect of the present invention the use of an LH-RH antagonist and one or more active agents as mentioned above is provided, wherein the LHRH antagonist is given for the induction treatment during 4 to 12 weeks and the treatment is repeated two or three times a year.

Claims :

1. In the method of therapeutic management of extrauterine proliferation of endometrial tissue, chronic pelvic pain and/or fallopian tube obstruction (FTO), the improvement consisting of administration of an LHRH antagonist in the form of a short-term induction treatment for a period of about 4 to 12 weeks to a patient in need of such treatment, whereby subsequently the administration of the LHRH antagonist is ceased.

2. A method according to claim 1 wherein the LHRH antagonist is administered such that the estrogen serum concentration level is between about 35 pg/ml and about 80 pg/ml, preferably between about 45–75 pg/ml, more preferably about 50-75 pg/ml.

3. A method according to claim 1 wherein the short-term induction treatment with the LHRH antagonist is followed by administration of a contraceptive, preferably an oral contraceptive.

4. A method according to claim 1 wherein the short-term induction treatment with the LHRH antagonist is followed by administration of a non-steroidal anti-rheumatic agent.

5. A method according to claim 1 wherein the short-term induction treatment with the LHRH antagonist is followed by administration of an analgetic.

6. A method according to claim 1 wherein the short-term induction treatment with the LHRH antagonist is followed by administration of an androgen other than a 17-alpha-alkyl substituted testosterone.

7. A method according to claim 1 wherein the short-term induction treatment with the LHRH antagonist is followed by the combined or separate administration of one or more active agents selected from the group consisting of a contraceptive, preferably an oral contraceptive, a non-steroidal anti-rheumatic agent, an

analgetic, an androgen other than a 17-alpha-alkyl substituted testosterone or any combinations thereof.

8. A method according to claim 1 wherein the LHRH antagonist is administered starting in the early to mid follicular phase, preferably on cycle day one to three.

9. A method according to claim 1 wherein the LHRH antagonist is selected from the group consisting of cetrorelix, teverelix, ganirelix, antide, abarelix and D-63153.

10. A method according to claim 1 wherein the LHRH antagonist is administered during the short-term induction treatment for about 4 to 12 weeks at a weekly dose of about 3 to 10 mg per week.

11. A method according to claim 1 wherein the LHRH antagonist is administered during the short-term induction treatment for about 4 to 12 weeks at a daily dose of about 0.25 mg to 0.5 mg/day.

12. A method according to claim 1 wherein the LHRH antagonist is administered during the short-term induction treatment for about 4 to 12 weeks at a monthly dose of about 12 to 40 mg per month.

13. A method according to claim 1 wherein the LHRH antagonist is given for the induction treatment during about 4 to 12 weeks and the treatment is repeated two or three times a year.

14. A pharmaceutical composition for treating extrauterine proliferation of endometrial tissue, chronic pelvic pain and/or fallopian tube obstruction (FTO) comprising an LHRH antagonist and optionally one or more agents selected from the group consisting of a contraceptive, preferably an oral contraceptive, a non-steroidal anti-rheumatic agent, an analgetic, an androgen other than a 17-alpha-alkyl substituted testosterone or any combinations thereof, optionally together with pharmaceutically acceptable excipients, whereby the LH-RH antagonist is administered to a patient in need thereof in a short term induction treatment for a

period of about 4 to 12 weeks, then the administration of the LH-RH antagonist is ceased and optionally the one or more agents selected from the group consisting of a contraceptive, preferably an oral contraceptive, a non-steroidal anti-rheumatic agent, an analgetic, an androgen other than a 17-alpha-alkyl substituted testosterone or any combinations thereof, are administered together or separately to the patient.

15. Pharmaceutical composition according to claim 14 wherein the LHRH antagonist is administered such that the estrogen serum concentration level is between about 35 pg/ml and about 80 pg/ml, preferably between about 45–75 pg/ml, more preferably about 50-75 pg/ml.

16. Pharmaceutical composition according to claims 14 or 15 wherein the short-term induction treatment with the LHRH antagonist is followed by administration of a contraceptive, preferably an oral contraceptive.

17. Pharmaceutical composition according to any one of the claims 14 to 16 wherein the short-term induction treatment with the LHRH antagonist is followed by administration of a non-steroidal anti-rheumatic agent.

18. Pharmaceutical composition according to any one of the claims 14 to 17 wherein the short-term induction treatment with the LHRH antagonist is followed by administration of an analgetic.

19. Pharmaceutical composition according to any one of the claims 14 to 18 wherein the short-term induction treatment with the LHRH antagonist is followed by administration of an androgen other than a 17-alpha-alkyl substituted testosterone.

20. Pharmaceutical composition according to any one of the claims 14 to 19 wherein the short-term induction treatment with the LHRH antagonist is followed by the combined or separate administration of one or more active agents selected from the group consisting of a contraceptive, preferably an oral contraceptive, a non-

steroidal anti-rheumatic agent, an analgetic, an androgen other than a 17-alpha-alkyl substituted testosterone or any combinations thereof.

21. Pharmaceutical composition according to any one of the claims 14 to 20 wherein the LHRH antagonist is administered starting in the early to mid follicular phase, preferably on cycle day one to three.

22. A pharmaceutical composition according to any one of claims 14 to 21 wherein the LHRH antagonist is selected from the group consisting of cetrorelix, teverelix, ganirelix, antide, abarelix and D-63153.

23. Pharmaceutical composition according to any one of claims 14 to 22 wherein the LHRH antagonist is administered during the short-term induction treatment for about 4 to 12 weeks at a weekly dose of about 3 to about 10 mg per week.

24. A pharmaceutical composition according to any one of claims 14 to 23 wherein the LHRH antagonist is administered during the short-term induction treatment for about 4 to 12 weeks at a daily dose of about 0.25 mg to about 0.5 mg/day.

25. Pharmaceutical composition according to any one of claims 14 to 24 wherein the LHRH antagonist is administered during the short-term induction treatment for about 4 to 12 weeks at a monthly dose of about 12 to 40 mg per month.

26. Pharmaceutical composition according to any one of claims 14 to 25 wherein the LHRH antagonist is given for the induction treatment during about 4 to 12 weeks and the treatment is repeated two or three times a year.

27. Pharmaceutical composition according to any one of claims 14 to 26, wherein the the one or more active agents selected from the group consisting of a contraceptive, preferably an oral contraceptive, a non-steroidal anti-rheumatic agent, an analgetic, an androgen other than a 17-alpha-alkyl substituted testosterone or any combinations thereof, are in the same or separate dosage forms.

28. Use of an LH-RH antagonist for the preparation of a medicament for the therapeutic management of extrauterine proliferation of endometrial tissue, chronic pelvic pain and/or fallopian tube obstruction (FTO), whereby the LHRH antagonist is administered in the form of a short-term induction treatment for a period of about 4 to 12 weeks to a patient in need of such treatment and then the administration of the LHRH antagonist is ceased.

29. Use of an LH-RH antagonist according to claim 28 wherein the LHRH antagonist is administered such that the estrogen serum concentration level is between about 35 pg/ml and about 80 pg/ml, preferably between about 45–75 pg/ml, more preferably about 50-75 pg/ml.

30. Use of an LH-RH antagonist according to claim 28 or 29 wherein the short-term induction treatment with the LHRH antagonist is followed by administration of a contraceptive, preferably an oral contraceptive.

31. Use of an LH-RH antagonist according to any one of claims 28 to 30 wherein the short-term induction treatment with the LHRH antagonist is followed by administration of a non-steroidal anti-rheumatic agent.

32. Use of an LH-RH antagonist according to any one of claims 28 to 31 wherein the short-term induction treatment with the LHRH antagonist is followed by administration of an analgetic.

33. Use of an LH-RH antagonist according to any one of claims 28 to 32 wherein the short-term induction treatment with the LHRH antagonist is followed by administration of an androgen other than a 17-alpha-alkyl substituted testosterone.

34. Use of an LH-RH antagonist according to any one of claims 28 to 33 wherein the short-term induction treatment with the LHRH antagonist is followed by the combined or separate administration of one or more active agents selected from

the group consisting of a contraceptive, preferably an oral contraceptive, a non-steroidal anti-rheumatic agent, an analgetic, an androgen other than a 17-alpha-alkyl substituted testosterone or any combinations thereof.

35. Use of an LH-RH antagonist according to any one of claims 28 to 34 wherein the LHRH antagonist is administered starting in the early to mid follicular phase, preferably on cycle day one to three.

36. Use of an LH-RH antagonist according to any one of claims 28 to 35 wherein the LHRH antagonist is selected from the group consisting of cetrorelix, teverelix, ganirelix, antide, abarelix and D-63153.

37. Use of an LH-RH antagonist according to any one of claims 28 to 36 wherein the LHRH antagonist is administered during the short-term induction treatment for about 4 to 12 weeks at a weekly dose of about 3 to about 10 mg per week.

38. Use of an LH-RH antagonist according to any one of claims 28 to 37 wherein the LHRH antagonist is administered during the short-term induction treatment for about 4 to 12 weeks at a daily dose of about 0.25 mg to about 0.5 mg/day.

39. Use of an LH-RH antagonist according to any one of claims 28 to 38 wherein the LHRH antagonist is administered during the short-term induction treatment for about 4 to 12 weeks at a monthly dose of about 12 to about 40 mg per month.

40. Use of an LH-RH antagonist according to any one of claims 28 to 39 wherein the LHRH antagonist is given for the induction treatment during about 4 to 12 weeks and the treatment is repeated two or three times a year.

41. Use of an LH-RH antagonist and one or more active agents selected from the group consisting of a contraceptive, preferably an oral contraceptive, a non-steroidal anti-rheumatic agent, an analgetic, an androgen other than a 17-alpha-alkyl substituted testosterone, or any combinations thereof, for the preparation of a medicament for the therapeutic management of extrauterine proliferation of

endometrial tissue, chronic pelvic pain and/or fallopian tube obstruction (FTO), whereby the LHRH antagonist is administered in the form of a short-term induction treatment for a period of about 4 to 12 weeks to a patient in need of such treatment, then the administration of the LHRH antagonist is ceased and the one or more active agent selected from the group consisting of a contraceptive, preferably an oral contraceptive, a non-steroidal anti-rheumatic agent, an analgetic, an androgen other than a 17-alpha-alkyl substituted testosterone, or any combinations thereof, are administered together or separately to the patient.

42. Use of an LH-RH antagonist and one or more active agents according to claim 41, wherein the LHRH antagonist is administered such that the estrogen serum concentration level is between about 35 pg/ml and about 80 pg/ml, preferably between about 45–75 pg/ml, more preferably about 50-75 pg/ml.

43. Use of an LH-RH antagonist and one or more active agents according according to claims 41 or 42 wherein the short-term induction treatment with the LHRH antagonist is followed by administration of a contraceptive, preferably an oral contraceptive.

44. Use of an LH-RH antagonist and one or more active agents according according according to any one of claims 41 to 43 wherein the short-term induction treatment with the LHRH antagonist is followed by administration of a non-steroidal anti-rheumatic agent.

45. Use of an LH-RH antagonist and one or more active agents according to any one of claims 41 to 44 wherein the short-term induction treatment with the LHRH antagonist is followed by administration of an analgetic.

46. Use of an LH-RH antagonist and one or more active agents according to any one of claims 41 to 45 wherein the short-term induction treatment with the LHRH antagonist is followed by administration of an androgen other than a 17-alpha-alkyl substituted testosterone.

47. Use of an LH-RH antagonist and one or more active agents according to any one of claims 41 to 46 wherein the short-term induction treatment with the LHRH antagonist is followed by the combined or separate administration of one or more active agents selected from the group consisting of a contraceptive, preferably an oral contraceptive, a non-steroidal anti-rheumatic agent, an analgetic, an androgen other than a 17-alpha-alkyl substituted testosterone or any combinations thereof.

48. Use of an LH-RH antagonist and one or more active agents according to any one of claims 41 to 47 wherein the LHRH antagonist is administered starting in the early to mid follicular phase, preferably on cycle day one to three.

49. Use of an LH-RH antagonist and one or more active agents according to any one of claims 41 to 48 wherein the LHRH antagonist is selected from the group consisting of cetrorelix, teverelix, ganirelix, antide, abarelix and D-63153.

50. Use of an LH-RH antagonist and one or more active agents according to any one of claims 41 to 49 wherein the LHRH antagonist is administered during the short-term induction treatment for about 4 to 12 weeks at a weekly dose of about 3 to 10 mg per week.

51. Use of an LH-RH antagonist and one or more active agents according to any one of claims 41 to 50 wherein the LHRH antagonist is administered during the short-term induction treatment for about 4 to 12 weeks at a daily dose of about 0.25 mg to 0.5 mg/day.

52. Use of an LH-RH antagonist and one or more active agents according to any one of claims 41 to 51 wherein the LHRH antagonist is administered during the short-term induction treatment for about 4 to 12 weeks at a monthly dose of about 12 to 40 mg per month.

53. Use of an LH-RH antagonist and one or more active agents according to any one of claims 41 to 52 wherein the LHRH antagonist is given for the induction treatment during about 4 to 12 weeks and the treatment is repeated two or three times a year.

Figure 1

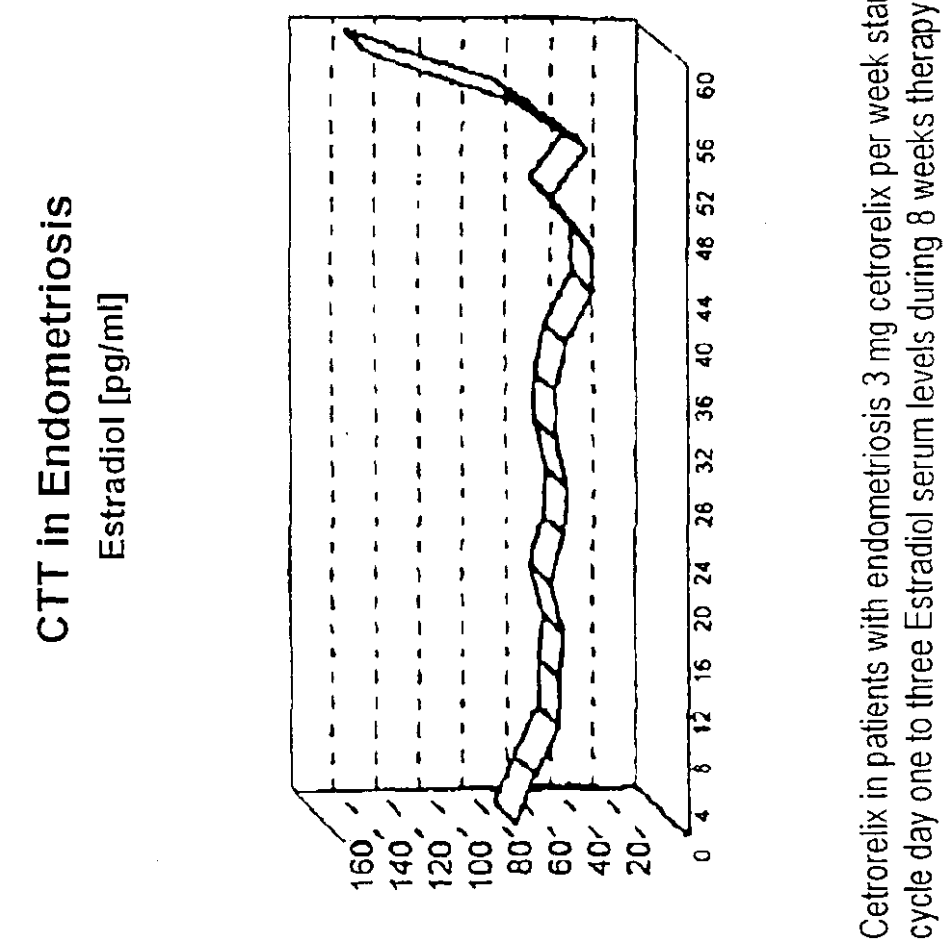
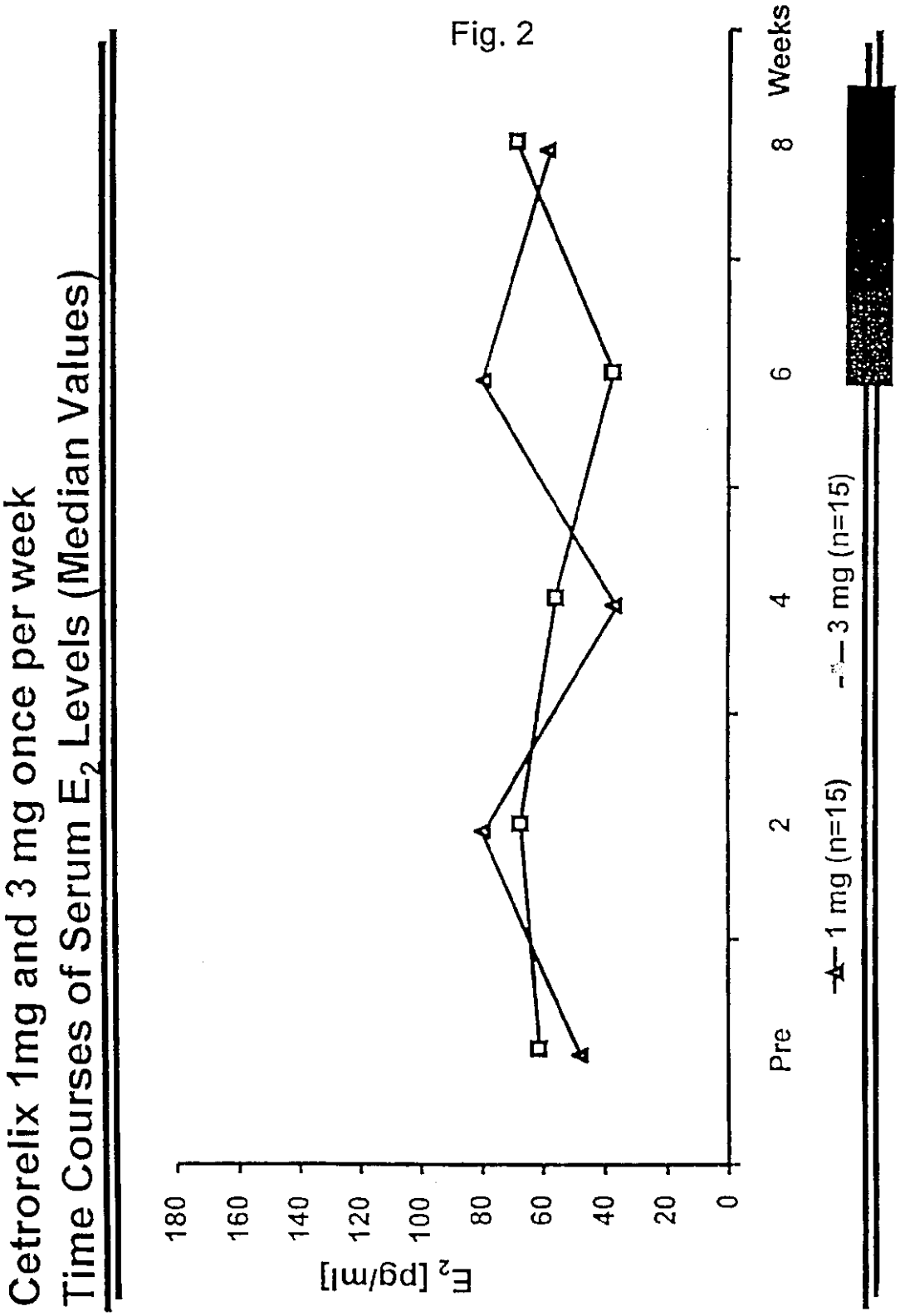

CTT in Endometriosis
Estradiol [pg/ml]
160
140
120
100
80
60
40
20
0
4
8
12
16
20
24
28
32
36
40
44
48
52
56
60
Cetrorelix in patients with endometriosis 3 mg cetrorelix per week starting on cycle day one to three Estradiol serum levels during 8 weeks therapy

Fig. 2


Cetrorelix 1mg and 3 mg once per week
Time Courses of Serum E_2 Levels (Median Values)
E_2 [pg/ml]
180
160
140
120
100
80
60
40
20
0
Pre
2
4
6
8
Weeks
1 mg (n=15)
3 mg (n=15)

[19]中华人民共和国国家知识产权局

[51]Int. Cl[7]
A61K 38/09
A61P 15/00

[12]发明专利申请公开说明书

[21]申请号 00813196.1

[43]公开日 2002年10月23日

[11]公开号 CN 1376070A

[22]申请日 2000.9.20 [21]申请号 00813196.1
[30]优先权
[32]1999.9.23 [33]US [31]60/155,478
[86]国际申请 PCT/EP00/09212 2000.9.20
[87]国际公布 WO01/21194 英 2001.3.29
[85]进入国家阶段日期 2002.3.21
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权利要求书 6 页 说明书 13 页 附图页数 2 页

[54]发明名称 用于治疗子宫内膜组织子宫外增生、慢性骨盆疼痛和输卵管梗阻的方法

[57]摘要

本发明提供了通过用LH-RH拮抗剂短期诱导治疗4至12周来治疗子宫内膜组织子宫外增生、慢性骨盆疼痛和输卵管梗阻的方法。按照本发明的另一方面，短期LH-RH治疗之后，联合或单独给予一种或多种选自避孕药、优选口服避孕药、非甾族抗风湿剂、止痛剂、除17-α-烷基取代的睾酮外的雄激素或它们的任意组合的活性剂。按照本发明进一步的方面，提供了含有LHRH拮抗剂和一种或多种选自避孕药、优选口服避孕药、非甾族抗风湿剂、止痛剂、除17-α-烷基取代的睾酮外的雄激素或它们的任意组合的活性剂的药物组合物。

ISSN1008-4274

权 利 要 求 书

1. 在治疗子宫内膜组织子宫外增生、慢性骨盆疼痛和/或输卵管梗阻(FTO)的方法中，由下述内容构成的改进：以短期诱导治疗的形式，给予需要此治疗的患者 LHRH 拮抗剂大约 4 至 12 周，然后停止给予 LHRH 拮抗剂。

2. 按照权利要求 1 所述的方法，其中给予 LHRH 拮抗剂使雌激素的血清浓度水平在大约 35 pg/ml 至大约 80 pg/ml 之间，优选大约 45-75 pg/ml，特别优选大约 50-75 pg/ml。

3. 权利要求 1 所述的方法，其中用 LHRH 拮抗剂短期诱导治疗之后，给予避孕药，优选口服避孕药。

4. 按照权利要求 1 所述的方法，其中用 LHRH 拮抗剂短期诱导治疗之后，给予非甾族抗风湿剂。

5. 权利要求 1 所述的方法，其中用 LHRH 拮抗剂短期诱导治疗之后，给予止痛剂。

6. 权利要求 1 所述的方法，其中用 LHRH 拮抗剂短期诱导治疗之后，给予除 17-α-烷基取代的睾酮外的雄激素。

7. 权利要求 1 所述的方法，其中用 LHRH 拮抗剂短期诱导治疗之后，联合或单独给予一种或多种选自避孕药、优选口服避孕药、非甾族抗风湿剂、止痛剂、除 17-α-烷基取代的睾酮外的雄激素或它们的任意组合的活性剂。

8. 权利要求 1 所述的方法，其中在卵泡期的早期至中期开始给予 LHRH 拮抗剂，优选在周期的第 1 至 3 天。

9. 权利要求 1 所述的方法，其中 LHRH 拮抗剂选自西曲瑞克、teverelix、加尼瑞克、antide、abarelix 和 D-63153。

10. 权利要求 1 所述的方法，其中在短期诱导治疗大约 4 至 12 周的期间中，以大约 3 至 10mg/周的周剂量给予 LHRH 拮抗剂。

11. 权利要求 1 所述的方法，其中在短期诱导治疗大约 4 至 12 周的期间中，以大约 0.25 至 0.5 mg/日的日剂量给予 LHRH 拮抗剂。

12. 权利要求 1 所述的方法，其中在短期诱导治疗大约 4 至 12 周的期间中，以 12 至 40mg/月的月剂量给予 LHRH 拮抗剂。

13. 权利要求 1 所述的方法，其中给予 LHRH 拮抗剂用于短期诱导治疗大约 4 至 12 周，并且此治疗一年重复 2 或 3 次。

14. 用于治疗子宫内膜组织子宫外增生、慢性骨盆疼痛和/或输卵管梗阻(FTO)的药物组合物，其含有 LHRH 拮抗剂和任选的一种或多种选自避孕药、优选口服避孕药、非甾族抗风湿剂、止痛剂、除 17-α-烷基取代的睾酮外的雄激素或它们的任意组合的成分，以及任选的药学上可接受的赋形剂，由此，在短期诱导治疗约 4 至 12 周的期间中给予需要的患者 LH-RH 拮抗剂，然后停止给予 LH-RH 拮抗剂，并且任选地一起或单独地给予患者一种或多种选自避孕药、优选口服避孕药、非甾族抗风湿剂、止痛剂、除 17-α-烷基取代的睾酮外的雄激素或它们的任意组合的成分。

15. 权利要求 14 所述的药物组合物，其中给予 LHRH 拮抗剂使雌激素的血清浓度水平在大约 35 pg/ml 至大约 80 pg/ml 之间，优选大约 45-75 pg/ml，特别优选大约 50-75 pg/ml。

16. 权利要求 14 或 15 所述的药物组合物，其中用 LHRH 拮抗剂短期诱导治疗之后，给予避孕药，优选口服避孕药。

17. 权利要求 14 至 16 任一项中所述的药物组合物，其中用 LHRH 拮抗剂短期诱导治疗之后，给予非甾族抗风湿剂。

18. 权利要求 14 至 17 任一项中所述的药物组合物，其中用 LHRH 拮抗剂短期诱导治疗之后，给予止痛剂。

19. 权利要求 14 至 18 任一项中所述的药物组合物，其中用 LHRH 拮抗剂短期诱导治疗之后，给予除 17-α-烷基取代的睾酮外的雄激素。

20. 权利要求 14 至 19 任一项所述的药物组合物，其中用 LHRH 拮抗剂短期诱导治疗之后，联合或单独给予一种或多种选自避孕药、优选口服避孕药、非甾族抗风湿剂、止痛剂、除 17-α-烷基取代的睾酮外的雄激素或它们的任意组合的活性剂。

21. 权利要求 14 至 20 任一项中所述的药物组合物，其中在卵泡期的早期至中期开始给予 LHRH 拮抗剂，优选在周期的第 1 至 3 天。

22. 权利要求 14 至 21 任一项中所述的药物组合物，其中 LHRH 拮抗剂选自西曲瑞克、teverelix、加尼瑞克、antide、abarelix 和 D-63153。

23. 权利要求 14 至 22 任一项中所述的药物组合物，其中在短期诱导治疗大约 4 至 12 周的期间中，以大约 3 至大约 10mg/周的周剂量给予 LHRH 拮抗剂。

24. 权利要求 14 至 23 任一项中所述的药物组合物，其中在短期诱导治疗大约 4 至 12 周的期间中，以大约 0.25 至大约 0.5 mg/日的日剂量给予 LHRH 拮抗剂。

25. 权利要求 14 至 24 任一项中所述的药物组合物，其中在短期诱导治疗大约 4 至 12 周的期间中，以大约 12 至 40mg/月的月剂量给予 LHRH 拮抗剂。

26. 权利要求 14 至 25 任一项中所述的药物组合物，其中给予 LHRH 拮抗剂用于诱导治疗大约 4 至 12 周，并且此治疗一年重复 2 或 3 次。

27. 权利要求 14 至 26 任一项所述的药物组合物，其中选自避孕药、优选口服避孕药、非甾族抗风湿剂、止痛剂、除 17-α-烷基取代的睾酮外的雄激素或它们的任意组合的一种或多种活性剂呈相同或各自的剂型。

28. LH-RH 拮抗剂用于制备治疗子宫内膜组织子宫外增生、慢性骨盆疼痛和/或输卵管梗阻(FTO)的药物的用途，由此，以短期诱导治疗的形式给予需要这样治疗的患者 LH-RH 拮抗剂大约 4 至 12 周，然后停止给予 LH-RH 拮抗剂。

29. 权利要求 28 所述的 LH-RH 拮抗剂的用途，其中给予 LHRH 拮抗剂使雌激素的血清浓度水平在大约 35 pg/ml 至大约 80 pg/ml 之间，优选大约 45-75 pg/ml，特别优选大约 50-75 pg/ml。

30. 权利要求 28 或 29 所述的 LH-RH 拮抗剂的用途，其中用 LHRH 拮抗剂短期诱导治疗之后，给予避孕药，优选口服避孕药。

31. 权利要求 28 至 30 任一项中所述的 LH-RH 拮抗剂的用途，其中用 LHRH 拮抗剂短期诱导治疗之后，给予非甾族抗风湿剂。

32. 权利要求 28 至 31 任一项中所述的 LH-RH 拮抗剂的用途，其中

用 LHRH 拮抗剂短期诱导治疗之后，给予止痛剂。

33. 权利要求 28 至 32 任一项中所述的 LH-RH 拮抗剂的用途，其中用 LHRH 拮抗剂短期诱导治疗之后，给予除 17-α-烷基取代的睾酮外的雄激素。

34. 权利要求 28 至 33 任一项中所述的 LH-RH 拮抗剂的用途，其中用 LHRH 拮抗剂短期诱导治疗之后，联合或单独给予一种或多种选自避孕药、优选口服避孕药、非甾族抗风湿剂、止痛剂、除 17-α-烷基取代的睾酮外的雄激素或它们的任意组合的活性剂。

35. 权利要求 28 至 34 任一项中所述的 LH-RH 拮抗剂的用途，其中在卵泡期的早期至中期开始给予 LHRH 拮抗剂，优选在周期的第 1 至 3 天。

36. 权利要求 28 至 35 任一项中所述的 LH-RH 拮抗剂的用途，其中 LHRH 拮抗剂选自西曲瑞克、teverelix、加尼瑞克、antide、abarelix 和 D-63153。

37. 权利要求 28 至 36 任一项中所述的 LH-RH 拮抗剂的用途，其中在短期诱导治疗大约 4 至 12 周的期间中，以大约 3 至大约 10mg/周的周剂量给予 LHRH 拮抗剂。

38. 权利要求 28 至 37 任一项中所述的 LH-RH 拮抗剂的用途，其中在短期诱导治疗大约 4 至 12 的期间周中，以大约 0.25 至大约 0.5 mg/日的日剂量给予 LHRH 拮抗剂。

39. 权利要求 28 至 38 任一项中所述的 LH-RH 拮抗剂的用途，其中在短期诱导治疗大约 4 至 12 周的期间中，以大约 12 至大约 40mg/月的月剂量给予 LHRH 拮抗剂。

40. 权利要求 28 至 39 任一项中所述的 LH-RH 拮抗剂的用途，其中给予 LHRH 拮抗剂用于诱导治疗大约 4 至 12 周，并且此治疗一年重复 2 或 3 次。

41. LH-RH 拮抗剂和一种或多种选自避孕药、优选口服避孕药、非甾族抗风湿剂、止痛剂、除 17-α-烷基取代的睾酮外的雄激素或它们的任意组合的活性剂用于制备治疗子宫内膜组织子宫外增生、慢性骨盆疼痛和/或输卵管梗阻(FTO)的药物的用途，由此以短期诱导治疗的形式给予

需要此治疗的患者 LHRH 拮抗剂大约 4 至 12 周，然后停止给予 LHRH 拮抗剂，并且一起或单独地给予患者一种或多种选自避孕药、优选口服避孕药、非甾族抗风湿剂、止痛剂、除 17-α-烷基取代的睾酮外的雄激素或它们的任意组合的活性剂。

42. 权利要求 41 中所述的 LH-RH 拮抗剂和一种或多种活性剂的用途，其中给予 LHRH 拮抗剂使雌激素的血清浓度水平在大约 35 pg/ml 至大约 80 pg/ml 之间，优选大约 45-75 pg/ml，特别优选大约 50-75 pg/ml。

43. 权利要求 41 或 42 中所述的 LH-RH 拮抗剂和一种或多种活性剂的用途，其中用 LHRH 拮抗剂短期诱导治疗之后，给予避孕药，优选口服避孕药。

44. 权利要求 41 至 43 任一项中所述的 LH-RH 拮抗剂和一种或多种活性剂的用途，其中用 LHRH 拮抗剂短期诱导治疗之后，给予非甾族抗风湿剂。

45. 权利要求 41 至 44 任一项中所述的 LH-RH 拮抗剂和一种或多种活性剂的用途，其中用 LHRH 拮抗剂短期诱导治疗之后，给予止痛剂。

46. 权利要求 41 至 45 任一项中所述的 LH-RH 拮抗剂和一种或多种活性剂的用途，其中用 LHRH 拮抗剂短期诱导治疗之后，给予除 17-α-烷基取代的睾酮外的雄激素。

47. 权利要求 41 至 46 任一项中所述的 LH-RH 拮抗剂和一种或多种活性剂的用途，其中用 LHRH 拮抗剂短期诱导治疗之后，联合或单独给予一种或多种选自避孕药、优选口服避孕药、非甾族抗风湿剂、止痛剂、除 17-α-烷基取代的睾酮外的雄激素或它们的任意组合的活性剂。

48. 权利要求 41 至 47 任一项中所述的 LH-RH 拮抗剂和一种或多种活性剂的用途，其中在卵泡期的早期至中期开始给予 LHRH 拮抗剂，优选在周期的第 1 至 3 天。

49. 权利要求 41 至 48 任一项中所述的 LH-RH 拮抗剂和一种或多种活性剂的用途，其中 LHRH 拮抗剂选自西曲瑞克、teverelix、加尼瑞克、antide、abarelix 和 D-63153。

50. 权利要求 41 至 49 任一项中所述的 LH-RH 拮抗剂和一种或多种

活性剂的用途，其中在短期诱导治疗大约 4 至 12 周的期间中，以大约 3 至 10mg/周的周剂量给予 LHRH 拮抗剂。

51. 权利要求 41 至 50 任一项中所述的 LHRH 拮抗剂和一种或多种活性剂的用途，其中在短期诱导治疗大约 4 至 12 周的期间中，以大约 0.25 至 0.5 mg/日的日剂量给予 LHRH 拮抗剂。

52. 权利要求 41 至 51 任一项中所述的 LH-RH 拮抗剂和一种或多种活性剂的用途，其中在短期诱导治疗大约 4 至 12 周的期间中，以大约 12 至 40mg/月的月剂量给予 LHRH 拮抗剂。

53. 权利要求 41 至 52 任一项中所述的 LH-RH 拮抗剂和一种或多种活性剂的用途，其中给予 LHRH 拮抗剂用于诱导治疗大约 4 至 12 周，并且此治疗一年重复 2 或 3 次。

说　明　书

用于治疗子宫内膜组织子宫外增生、慢性骨盆疼痛和输卵管梗阻的方法

发明的技术领域

子宫内膜异位症是妇科患者诊断中最常见的病理之一。例如，在英国和美国具有妇科症状的10%至25%的妇女患有此病。通常通过对盆腔器官的出血或纤维变性病灶的腹腔镜观察进行临床诊断。异位的子宫内膜组织随着卵巢激素发生周期性变化。来自于子宫内膜沉积的周期性出血有助于局部的炎症性反应。子宫内膜异位症通常发生于育龄妇女，发病率至少为1%(参见Shaw,R. W.(1993),子宫内膜异位症图集(An Atlas of Endometriosis, The Parthenon Publishing Group)。

子宫内膜异位症通常分为子宫内子宫内膜异位(子宫腺肌病)、子宫外子宫内膜异位和生殖器官外子宫内膜异位。

慢性骨盆疼痛可以与子宫内膜异位症关联发生，或者以一种独立的疾病发生。

输卵管梗阻(FTO)是一种较常见的疾病，可以达到输卵管不孕症情况的20%(参见Winfield,A. C.等,子宫输卵管造影术中明显的角闭塞：通过胰升糖素反转(Apparent cornual occlusion in hysterosalpingography:Reversal by glucagon)，美国X线学杂志(AJR Am J Roentgenol)1982;139:525-527)。

背景资料和现有技术

Sampson提出：月经的反流和随后的子宫内膜组织在腹膜面的植入导致子宫内膜异位症[Sampson,J. A.(1927)，子宫内膜组织的月经播散进入腹膜腔所致腹膜的子宫内膜异位症(Peritoneal endometriosis due to menstrual dissemination of the endometrial tissue into the peritoneal cavitiy)．美国妇产科学杂志(Am.J.Obstet.Gyneol.)，

14,422]。

子宫内膜异位症的发病机理可以与几种病原学因素有关:

Dmowski 等提出: 遗传和免疫因素导致子宫内膜异位症[Dmowski,W.P.,Steele,R.W.和Baker,G.F.(1981),子宫内膜异位症中的细胞免疫缺陷(Deficient cellular immunity in endometriosis),美国妇产科学杂志(Am.J.Obstet.Gyneol.),141,377]。

血管和淋巴管的远位栓塞已经证明和解释了腹膜腔外例如皮肤、肺和肾的子宫内膜异位症的(罕见)发现。

米勒管上排列的细胞产生于原始细胞,它们分化为腹膜细胞和位于卵巢表面的细胞。有人提出:这些成熟细胞经历去分化(de-differentiation)返回它们的原始起源并然后转化为子宫内膜细胞[Levander,G.(1941),通过诱导的骨生成(Bone formation by induction),An.experimental study.Arch.Klin.Chir.,202,497]。

有人报道:痛经、急性或慢性骨盆疼痛、性交疼痛和不孕症是最常见的临床症状。

FTO 代表来源于雌激素敏感性疾病的初步的内部闭塞或外部压迫的基础的病理学的一组异种组,例如子宫内膜异位、子宫腺肌病、输卵管子宫内膜异位和肌瘤。除了腹腔镜外,也常通过子宫输卵管造影术来诊断FTO。

治疗的首选包括腹腔镜下去除子宫内膜损害。这一步骤后可以用达那唑或LHRH激动剂治疗(6个月)。接受达那唑治疗的妇女可能会遭受胃肠道和肝脏疾病以及严重的产生雄性特征的副作用。

还有人从理论的观点提出:应用通过给予LHRH拮抗剂的立即抑制治疗子宫内膜异位和子宫肌瘤,以缩短治疗时间和加快改善自觉症状[Th.Reissmann 等,人体生殖杂志(Human Reprodution),第10卷,第8期,第1974-1981页,(1995)]。

而且,Hodgen在美国专利5,658,884中讲授了一种通过减少雌激素供应治疗性腺依赖性疾病的方案,该方案是通过以一种有效抑制子宫内膜组织增生而基本上不停止内源性雌激素产生的剂量,长期给予GnRH拮

抗剂6个月或更长时间。为了此目的,Hodgen讲授了这样一种方案或GnRH拮抗剂的剂量，以获得24小时血清雌二醇的水平在大约25至50 pg/ml范围内，优选大约35至45 pg/ml。但是，Hodgen没有描述雌二醇血清水平在50至75 pg/ml之间波动。而且，Hodgen在美国专利5,658,884中仅仅讲授了一种连续的长期治疗（以每日或周期性为基础，后者的含意是每周或每月给药），没有讲授仅仅4至12周的短期诱导治疗。而且，Hodgen没有描述在治疗子宫内膜异位症中包含了GnRH拮抗剂的任何结合疗法。此治疗仅仅描述于猴子上,而且还包括为提供30至50 pg/ml的24小时平均血清雌二醇水平所进行的昂贵和重复的孕酮攻击实验。

LHRH-竞争疗法突然发挥作用的结果是在某些天可能发生症状加剧。需要随后的延长治疗以避免子宫内膜组织再增生、激素戒断症状以及骨骼脱矿质的发生。

因此，有效的药物疗法应当立即减少腹腔镜外科手术后存在的残留子宫外的子宫内膜组织。治疗时间应当仅仅为4至12周，没有任何主要的激素戒断症状出现或卵巢囊肿形成。

LHRH拮抗剂产生立即开始的激素抑制，并因此在短时间内良性妇科肿瘤、例如子宫纤维瘤减少[人体生殖杂志(Human Reprodution)1998,13]。

本发明目的

本发明涉及子宫内膜组织子宫外增生的药物治疗的改进，即对具有子宫内膜异位症临床症状的患者给予LHRH拮抗剂，其改进由下列组成:

立即减少异位的子宫内膜组织

立即停止症状例如严重的疼痛、慢性骨盆疼痛和痛经

防止疾病的任何进展

避免出现激素戒断症状

预防卵巢囊肿形成、骨骼脱矿质以及胃肠道或肝脏疾病

本发明的药物疗法可以在卵泡期的早期至中期开始,优选在周期的第1至3天。在治疗期间，雌二醇的血清浓度水平保持在35至80 pg/ml

之间，优选大约 45 至 75 pg/ml 之间，特别优选大约 50 至 75 pg/ml 之间。LHRH 拮抗剂仅仅给予 4 至 12 周(短期诱导治疗)，可通过每日、每周或者通过每月给药。按照本发明，在短期诱导治疗之后，给予避孕药、非甾族抗风湿剂、止痛剂、除 17-α-烷基取代的睾酮之外的雄激素或它们的任意组合。

本发明概述

在使用 LHRH 拮抗剂治疗子宫外子宫内膜组织中，治疗在月经周期的第 1 至 3 天开始。在开始 LHRH 拮抗剂治疗之前，通过腹腔镜进行诊断。

在严重疼痛的情况下，可以先不进行腹腔镜检查而开始 LHRH 拮抗剂治疗。

治疗将继续直至临床症状消失并且看不到子宫内膜增生为止。由于立即开始的促性腺激素 LH 和 FSH 以及性甾族化合物雌二醇和孕酮的抑制，没有发生子宫内膜的进一步增生。在 4 至 12 周的治疗中，良性肿瘤或其它的性甾族化合物依赖性损害像子宫内膜异位有所减少。由于不是突然发挥作用，因此没有形成卵巢囊肿。

而且，当雌二醇的值保持在早卵泡期的 35 至 80 pg/ml、优选大约 45 至 75 pg/ml、特别优选约 50 至 75 pg/ml 的范围之间，并且没有进一步增加或减少时，没有看到激素戒断症状。不需要滴定 LHRH 拮抗剂的剂量，例如通过进行昂贵的孕酮攻击实验。

治疗子宫内膜组织子宫外增生的方法，按照本发明其改进包括:

立即减少异位的子宫内膜组织

防止疾病的任何进展

避免出现激素戒断症状

预防卵巢囊肿形成、骨骼脱矿质以及胃肠道或肝脏疾病

在周期的第 1 至 3 天开始药物治疗，并且通过给予 LHRH 拮抗剂使雌二醇的水平在整个治疗时间内保持在早卵泡期的数值，其中拮抗剂优选西曲瑞克、teverelix、加尼瑞克、antide 或 abarelix。此拮抗剂还可以是 1999 年 3 月 11 日申请的德国专利申请说明书第 19911 771.3 中所

述的 LHRH 拮抗剂 D-63153(Ac-D-Nal-D-pCl-Phe-D-Pal-Ser-N-Me-Tyr-D-Hci-Nle-Arg-Pro-D-Ala-NH2)。

可以以 3 至 10mg/周的周剂量给予 LHRH 拮抗剂 4 至 12 周，或者以 0.25 至 0.5 mg/日的日剂量给予 LHRH 拮抗剂 4 至 12 周。

还可以以 12 至 40mg/月的月剂量给予 LHRH 拮抗剂 4 至 12 周。

在一个重复的治疗中，LHRH 拮抗剂可以给予 4 至 12 周，并且此治疗一年重复 2 或 3 次，因此在短期诱导治疗之后不能直接接着一个重复治疗。通常在短期诱导治疗结束后和重复治疗开始前，有几周或几个月的一段时间，在此期间不给予 LHRH 拮抗剂。

为了证明在调整的 LHRH-拮抗剂治疗下保持低的雌二醇分泌以使治疗性抑制出现但没有戒断症状的可行性，对被证实具有子宫内膜异位的 9 名患者，用 3 mg 西曲瑞克醋酸盐皮下每周给药持续 8 周进行治疗。患者的依从性极好，从而避免了任何潮热或其他的戒断症状，并且通过第二次腹腔镜检查证实疾病没有任何发展，平均雌二醇血清浓度在 37 pg/ml 至 64 pg/ml 之间、优选 45-75 pg/ml 之间、特别优选大约 50-75 pg/ml 之间波动。组织学活检显示：在治疗结束时，没有子宫内膜增生。没有发现卵巢囊肿形成。

图 1 显示了从接受 3 mg 周剂量西曲瑞克(LHRH 拮抗剂)治疗 8 周的子宫内膜异位症患者中获得的达到早卵泡期数值（35 pg/ml 至 80 pg/ml、优选 45-75 pg/ml、特别优选大约 50-75 pg/ml）的连续的雌二醇水平抑制。在治疗结束时，获得了即时的和连续的雌二醇水平抑制，没有任何雌二醇戒断症状的迹象和子宫内膜增生。

图 2 显示了分别以每周一次 1 mg 和 3 mg 的周剂量给予西曲瑞克后的雌二醇的血清水平。雌二醇的血清水平在大约 35 pg/ml 至 80 pg/ml 之间，优选在大约 45-75 pg/ml 之间，特别优选在大约 50-75 pg/ml 之间。

具有独特症状疼痛的子宫内膜异位症患者正患有一种慢性疾病。治愈疗法意义上的外科方法以及抑制患者性甾族化合物分泌的药物治疗通常只能带来暂时的改善。不适的复发率是非常高的，在结束治疗 5 年内

大约为 70% (Schweppe, 1999)。

同时，根本的外科疗法以及雌激素分泌的抑制带来了相当大的副作用。带有两侧附件切除的子宫切除术意义上的根本外科疗法对于年轻、绝经前期的妇女是不适宜的疗法。雌激素的慢性缺乏将导致下列自主(vegetative)症状：潮热、出汗、阴道干燥、感觉抑郁以及患骨质疏松症的危险。由于产生雄性特征的作用，用合成甾族化合物达那唑的替代疗法可以引起男性化症状。

对具有症状疼痛的子宫内膜异位症患者的药物治疗目的是获得没有副作用、特别是避免了雌激素抑制的消极作用，而且在治疗结束后长时间持续有效的治疗。这种 LHRH 拮抗剂作用的特殊的药理模式为子宫内膜异位症的治疗提供了新的可能性。

以适当剂量例如 3 mg Cetrotide®皮下/每周、每周给予 LHRH 拮抗剂，持续 8 周，可以导致雌激素分泌控制的抑制，以致于得到的血清浓度在大约 35 pg/ml 至 80 pg/ml 之间，优选约 45-75 pg/ml，特别优选约 50-75 pg/ml。在此血清浓度范围内，没有出现自主性症状。还可以避免骨质疏松症的发展。在此疾病的所有阶段（rAFS I-IV），症状性疼痛均将有效地抑制。在 rAFS I-II 阶段，可以注意到植入面积减少意义上的疾病的临床消退(Felberbaum 等, 2000)。

在本发明的一个优选实施例中，进行此治疗 8 至 12 周后，除非希望妊娠，患者可以服用避孕药，优选口服避孕药，更优选具有促孕激素成分的口服避孕药。在这些联合中，必须提到利奈孕酮 2 mg 和 0.04 mg 炔雌醇或者利奈孕酮 2.5 mg 和 0.05 mg 炔雌醇(例如 Yermonil®、Lyn-ratiopharm-Sequenz®)的联合。

在单独使用 LHRH 拮抗剂或联合使用甾族抗风湿剂和/或止痛剂短期诱导治疗之后，还可以使用除 17-α-烷基取代的睾酮外的雄激素、例如达那唑进行联合治疗。适宜的雄激素的实例为 halotestin™(氟甲睾酮)。

用避孕药、优选口服避孕药、优选其中含有促孕激素进行的治疗应当个体化地持续直到出现典型的疼痛感觉。由于这种避孕药、优选口服避孕药的促孕激素成分的作用，在此阶段，患者将会有比较少的月经出

血。而且，为了克服特别严重的月经前和月经期间的疼痛感觉，在此阶段，可以给予带有适宜的非甾族抗风湿性药物例如双氯芬酸、布洛芬、吲哚美辛、oxicam 衍生物或阿斯匹林的伴随药物。还可以给予止痛剂例如 flupirtinmaleat(Katadolon®)。

如果在用促孕激素避孕药、优选口服避孕药治疗期间还出现进一步的疼痛症状，可以重复如上所述的用适当剂量的 LHRH 拮抗剂的每日、每周或每月的治疗。关于相应的治疗选择的详细资料在下面给出。如果患者完全没有疼痛，治疗可以变为促孕激素避孕药、优选口服避孕药与作为伴随药物的适宜的非甾族抗风湿剂或止痛剂联合给药。

这种间断给予LHRH拮抗剂的疗法带来了新的并且富有创新的不受限制的治疗，并且没有副作用，而且这种治疗明显地降低了患者的治疗费用。

适宜于治疗的药物制剂

适宜于治疗子宫内膜组织子宫外增生、慢性骨盆疼痛和输卵管梗阻(FTO)的 LHRH 拮抗剂的药物制剂可以例如是

a) 浓度为 1 mg/1 ml 或更低的醋酸盐制剂，其中粉末可以溶于注射用水(Wfl)或葡糖酸(GA)中；
b) 浓度为 1.5 mg/1 ml 至 5.0 mg/1 ml、优选 2.5 mg/1 ml 的醋酸盐制剂，其中粉末可以溶于注射用水(Wfl)或葡糖酸(GA)中；
c) 浓度为 10 mg/1 ml 至 30 mg/1 ml、优选 15 mg/1 ml 的醋酸盐制剂，其中冻干粉末可以溶于葡糖酸(GA)或注射用水(Wfl)中。

按照本发明的一个方面，在治疗子宫内膜组织子宫外增生、慢性骨盆疼痛和/或输卵管梗阻(FTO)的方法中，提供的改进在于：以短期诱导治疗的形式给予需要此治疗的患者 LHRH 拮抗剂大约 4 至 12 周，然后停止给予此 LHRH 拮抗剂。

短期诱导治疗的时间为大约 4 至 12 周的含意是：治疗时间在大约 28 至大约 84 天之间，或从大约 1 个月至大约 3 个月。

按照本发明的另一个方面，在如上所述的方法中，提供了改进，其

中给予LHRH拮抗剂使雌激素的血清浓度水平在大约35 pg/ml至80 pg/ml之间，优选大约45-75 pg/ml，特别优选大约50-75 pg/ml。

按照本发明的另一个方面，在如上所述的方法中，提供了改进，其特征在于：用LHRH拮抗剂短期诱导治疗之后，给予避孕药，优选口服避孕药。

按照本发明的另一个方面，在如上所述的方法中，提供了改进，其特征在于：用LHRH拮抗剂短期诱导治疗之后，给予一种非甾族抗风湿剂。

按照本发明的另一个方面，如上所述的方法中，提供了改进，其特征在于：其中用LHRH拮抗剂短期诱导治疗之后，给予止痛剂。

按照本发明的另一个方面，在如上所述的方法中，提供了改进，其特征在于：用LHRH拮抗剂短期诱导治疗之后，给予除17-α-烷基取代的睾酮之外的雄激素。

按照本发明的另一个方面，在如上所述的方法中，提供了改进，其特征在于：用LHRH拮抗剂短期诱导治疗之后，联合或单独给予一种或多种选自避孕药、优选口服避孕药、非甾族抗风湿剂、止痛剂、除17-α-烷基取代的睾酮外的雄激素或它们的任意组合的活性剂。

按照本发明的另一个方面，在如上所述的方法中，提供了改进，其特征在于：在卵泡期的早期至中期开始给予LHRH拮抗剂，优选在周期的第1至3天。

按照本发明的另一个方面，在如上所述的方法中，提供了改进，其特征在于：LHRH拮抗剂选自西曲瑞克、teverelix、加尼瑞克、antide、abarelix和D-63153。

按照本发明的另一个方面，在如上所述的改进的方法，其特征在于：在短期诱导治疗4至12周的期间中，以3至10mg/周的周剂量给予LHRH拮抗剂。

按照本发明的另一个方面，在如上所述的方法中，提供了改进其特征在于：在短期诱导治疗4至12周的期间中，以0.25至0.5 mg/日的日剂量给予LHRH拮抗剂。

按照本发明的另一个方面，在如上所述的方法中，提供了改进，其

特征在于：在短期诱导治疗 4 至 12 周的期间中，以 12 至 40mg/月的月剂量给予 LHRH 拮抗剂。

按照本发明的另一个方面，在如上所述的方法中，提供了改进，其特征在于：给予 LHRH 拮抗剂用于诱导治疗 4 至 12 周，并且此治疗一年重复 2 或 3 次。

按照本发明的进一步的一个方面，提供了用于治疗子宫内膜组织子宫外增生、慢性骨盆疼痛和/或输卵管梗阻(FTO)的药物组合物，它含有 LHRH 拮抗剂和任选的一种或多种选自避孕药优选口服避孕药、非甾族抗风湿剂、止痛剂、除 17-α-烷基取代的睾酮外的雄激素或它们的任意组合的成分，以及任选的药学上可接受的赋形剂，由此，在短期诱导治疗大约 4 至 12 周中给予需要的患者 LH-RH 拮抗剂，然后停止给予此 LH-RH 拮抗剂，并且任选地一起或单独地给予患者一种或多种选自避孕药、优选口服避孕药、非甾族抗风湿剂、止痛剂、除 17-α-烷基取代的睾酮外的雄激素或它们的任意组合的成分。

适宜的赋形剂和剂型例如由 K. H. Bauer、K. H. Frö mming 和 C. FÜhrer，描述于 Lehrbuch der Pharmazeutischen Technologie，第 6 版，Stuttgart 1999，第 163-186 页（赋形剂）和第 227-386 页(剂型)中，包括引证于那里的参考文献。

LH-RH 拮抗剂可以例如经皮下（s. c. ）、肌肉内（i. m. ）或吸入给药。选自避孕药、优选口服避孕药、非甾族抗风湿剂、止痛剂、除 17-α-烷基取代的睾酮外的雄激素或它们的任意组合的成分可以以本领域中已知的方式给药（参见例如德国、欧洲或美国药典），优选口服或吸入。

按照本发明的另一方面，提供了如上所述的药物组合物，其中给予 LHRH 拮抗剂使雌激素的血清浓度水平在大约 35 pg/ml 至 80 pg/ml 之间，优选大约 45-75 pg/ml，特别优选大约 50-75 pg/ml。

按照本发明的另一方面，提供了如上所述的药物组合物，其中用 LHRH 拮抗剂短期诱导治疗之后，给予避孕药，优选口服避孕药。

按照本发明的另一方面，提供了如上所述的药物组合物，其中用 LHRH 拮抗剂短期诱导治疗之后，给予非甾族抗风湿剂。

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按照本发明的另一方面，提供了如上所述的药物组合物，其中在卵泡期的早期至中期开始给予 LHRH 拮抗剂，优选在周期的第 1 至 3 天。

按照本发明的另一方面，提供了如上所述的药物组合物，其中 LHRH 拮抗剂选自西曲瑞克、teverelix、加尼瑞克、antide、abarelix 和 D-63153。

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按照本发明的另一方面，提供了如上所述的药物组合物，其中在短期诱导治疗 4 至 12 周的期间中，以 0.25 至 0.5 mg/日的日剂量给予 LHRH 拮抗剂。

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按照本发明的另一方面，提供了如上所述的药物组合物，其中给予 LHRH 拮抗剂用于诱导治疗 4 至 12 周，并且此治疗一年重复 2 或 3 次。

按照本发明的另一方面，提供了如上所述的药物组合物，其中一种或多种选自避孕药、优选口服避孕药、非甾族抗风湿剂、止痛剂、除 17-α-烷基取代的睾酮外的雄激素或它们的任意组合的活性剂呈相同的或各自的剂型。

按照本发明的另一方面，提供了 LH-RH 拮抗剂用于制备治疗子宫内

膜组织子宫外增生、慢性骨盆疼痛和/或输卵管梗阻(FTO)的药物的用途，其中以短期诱导治疗大约 4 至 12 周的形式给予需要此治疗的患者 LHRH 拮抗剂，然后停止给予 LHRH 拮抗剂。

按照本发明的另一方面，提供了如上所述的 LH-RH 拮抗剂的用途，其中给予 LHRH 拮抗剂使雌激素的血清浓度水平在大约 35 pg/ml 至大约 80 pg/ml 之间，优选大约 45-75 pg/ml，特别优选大约 50-75 pg/ml。

按照本发明的另一方面，提供了如上所述的 LH-RH 拮抗剂的用途，其中用 LHRH 拮抗剂短期诱导治疗之后，给予避孕药，优选口服避孕药。

按照本发明的另一方面，提供了如上所述的 LH-RH 拮抗剂的用途，其中用 LHRH 拮抗剂短期诱导治疗之后，给予非甾族抗风湿剂。

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按照本发明的另一方面，提供了如上所述的 LH-RH 拮抗剂的用途，其中在卵泡期的早期至中期开始给予 LHRH 拮抗剂，优选在周期的第 1 至 3 天。

按照本发明的另一方面，提供了如上所述的 LH-RH 拮抗剂的用途，其中 LHRH 拮抗剂选自西曲瑞克、teverelix、加尼瑞克、antide、abarelix 和 D-63153。

按照本发明的另一方面，提供了如上所述的 LH-RH 拮抗剂的用途，其中在短期诱导治疗 4 至 12 周的期间中，以 3 至 10mg/周的周剂量给予 LHRH 拮抗剂。

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其中在短期诱导治疗 4 至 12 周的期间中，以 0.25 至 0.5 mg/日的日剂量给予 LHRH 拮抗剂。

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按照本发明的另一方面，提供了 LH-RH 拮抗剂和一种或多种选自一种避孕药优选口服避孕药、非甾族抗风湿剂、止痛剂、除 17-α-烷基取代的睾酮外的雄激素或它们的任意组合的活性剂用于制备治疗子宫内膜组织子宫外增生、慢性骨盆疼痛和/或输卵管梗阻(FTO)的药物的用途，其中以短期诱导治疗的形式给予需要此治疗的患者 LHRH 拮抗剂大约 4 至 12 周，然后停止给予此 LHRH 拮抗剂，并且将一种或多种选自避孕药、优选口服避孕药、非甾族抗风湿剂、止痛剂、除 17-α-烷基取代的睾酮外的雄激素或它们的任意组合的活性剂一同或单独患者。

按照本发明的另一方面，提供了如上所述的 LH-RH 拮抗剂和一种或多种活性剂的用途，其中给予 LHRH 拮抗剂使雌激素的血清浓度水平在大约 35 pg/ml 至大约 80 pg/ml 之间，优选约 45-75 pg/ml，特别优选大约 50-75 pg/ml。

按照本发明的另一方面，提供了如上所述的 LH-RH 拮抗剂和一种或多种活性剂的用途，其中用 LHRH 拮抗剂短期诱导治疗之后，给予避孕药，优选口服避孕药。

按照本发明的另一方面，提供了一种如上所述的 LH-RH 拮抗剂和一种或多种活性剂的用途，其中用 LHRH 拮抗剂短期诱导治疗之后，给予非甾族抗风湿剂。

按照本发明的另一方面，提供了如上所述的 LH-RH 拮抗剂和一种或多种活性剂的用途，其中用 LHRH 拮抗剂短期诱导治疗之后，给予止痛剂。

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多种活性剂的用途，其中用 LHRH 拮抗剂短期诱导治疗之后，给予除 17-α-烷基取代的睾酮外的雄激素。

按照本发明的另一方面，提供了如上所述的 LH-RH 拮抗剂和一种或多种活性剂的用途，其中用 LHRH 拮抗剂短期诱导治疗之后，联合或单独给予一种或多种选自避孕药、优选口服避孕药、非甾族抗风湿剂、止痛剂、除 17-α-烷基取代的睾酮外的雄激素或它们的任意组合的活性剂。

按照本发明的另一方面，提供了如上所述的 LH-RH 拮抗剂和一种或多种活性剂的用途，其中在卵泡期的早期至中期开始给予 LHRH 拮抗剂，优选在周期的第 1 至 3 天。

按照本发明的另一方面，提供了如上所述的 LH-RH 拮抗剂和一种或多种活性剂的用途，其中 LHRH 拮抗剂选自西曲瑞克、teverelix、加尼瑞克、antide、abarelix 和 D-63153。

按照本发明的另一方面，提供了如上所述的 LH-RH 拮抗剂和一种或多种活性剂的用途，其中在短期诱导治疗 4 至 12 周的期间中，以 3 至 10mg/周的周剂量给予 LHRH 拮抗剂。

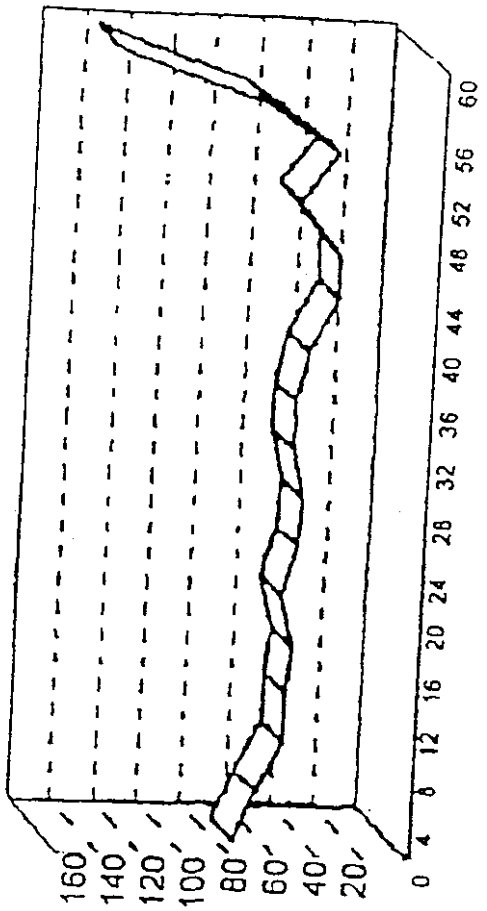
按照本发明的另一方面，提供了如上所述的 LH-RH 拮抗剂和一种或多种活性剂的用途，其中在短期诱导治疗 4 至 12 周的期间中，以 0.25 至 0.5 mg/日的日剂量给予 LHRH 拮抗剂。

按照本发明的另一方面，提供了如上所述的 LH-RH 拮抗剂和一种或多种活性剂的用途，其中在短期诱导治疗 4 至 12 周的期间中，以 12 至 40mg/月的月剂量给予 LHRH 拮抗剂。

按照本发明的另一方面，提供了如上所述的 LH-RH 拮抗剂和一种或多种活性剂的用途，其中给予 LHRH 拮抗剂用于短期诱导治疗 4 至 12 周，并且此治疗一年重复 2 或 3 次。

说 明 书 附 图

图 1



从周期的第 1 至 3 天开始，每周给予子宫内膜异位症的患者 3mg 西曲瑞克治疗 8 周期间的雌二醇血清水平

图 2

每周一次 1mg 和 3mg 西曲瑞克血清
E_2 水平（平均值）的时间进程