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(54) Title: A METHOD OF TREATING BENIGN GYNAECOLOGICAL DISORDERS AND A DRUG DELIVERY VEHICLE FOR USE IN SUCH A METHOD

(57) Abstract: One aspect of the present invention is concerned with a method of treating a benign gynaecological disorder in a female mammal using a drug delivery vehicle, said benign gynaecological disorders being selected from the group consisting of uterine leiomyomas, endometriosis, adenomyosis, functional menorrhagia and metrorrhagia, the method comprising intravaginal administration of the drug delivery vehicle to the female mammal suffering from the benign gynaecological disorder, said drug delivery vehicle containing a selective estrogen enzyme modulator (SEEM), wherein the method provides the SEEM in a therapeutically effective dosage to prevent or reduce symptoms of said benign gynaecological disorder, said SEEM being selected from the group consisting of aromatase inhibitors, cyclo-oxygenase 2 (COX-2) inhibitors, 17 ß-hydroxysteroid dehydrogenase type 1 inhibitors and combinations thereof. The present method is suitable for long term medical therapy of estrogen sensitive benign gynaecological disorders, particularly for pre- and peri-menopausal females and does not cause serious side-effects. Another aspect of the invention is concerned with a drug delivery vehicle for intravaginal use, comprising at least 10 µg of a SEEM selected from the group consisting of aromatase inhibitors, 17ß-hydroxysteroid dehydrogenase type 1 inhibitors and combinations thereof; and pharmaceutically acceptable excipient.

A METHOD OF TREATING BENIGN GYNAECOLOGICAL DISORDERS AND A DRUG DELIVERY VEHICLE FOR USE IN SUCH A METHOD

TECHNICAL FIELD

The present invention relates to a method of treating an estrogen sensitive benign gynaecological disorder in mammal females, especially a benign gynaecological disorder selected from the group consisting of uterine leiomyomas, endometriosis, adenomyosis, functional menorrhagia and metrorrhagia. More particularly the present invention relates to such a method comprising the administration of a drug delivery vehicle to a female mammal suffering from such a benign gynaecological disorder, said drug delivery vehicle containing a selective estrogen enzyme modulator (SEEM) selected from the group consisting of aromatase inhibitors, cyclo-oxygenase 2 (COX-2) inhibitors, 17β-hydroxysteroid dehydrogenase type 1 inhibitors and combinations thereof, wherein the method provides the SEEM in a therapeutically effective dosage to prevent or reduce symptoms of said benign gynaecological disorder.

"Selective estrogen enzyme modulator" is a term of the art as exemplified by an article written by Chetrite and Pasqualini (J of Steroid Biochem & Mol Biol 2001; 76; 95-104). SEEMs have in common that they have the capability to inhibit the *in vivo* biogenesis of estrogens, especially by inhibiting enzymes that are involved in or that affect the last steps of biosynthetic pathways that generate these estrogens.

Another aspect of the invention is concerned with a drug delivery vehicle which contains an aromatase inhibitor and/or a 17β-hydroxysteroid dehydrogenase type 1 inhibitor.and pharmaceutically acceptable excipient.

BACKGROUND OF THE INVENTION

Uterine leiomyomas (fibroids or myomas), benign clonal tumours, arise from smooth-muscle cells of the human uterus. They are clinically apparent in up to 25% of women and are the single most common indication for hysterectomy. They cause significant morbidity, including prolonged and heavy menstrual bleeding, pelvic pressure and pain, urinary problems, and, in rare cases, reproductive dysfunction.

The pathophysiology of myomas is not well understood. However, both genetic predisposition and steroid hormone concentrations have a role in the development and growth of these benign tumours. In addition, growth factors play an important role in fibrotic processes and angiogenesis. At least two distinct steps to myoma formation can be identified. First, normal myocytes have to be transformed into abnormal myocytes and secondly, these abnormal cells subsequently have to grow into clinically apparent tumours. Microscopic myomas have a high prevalence, meaning that the first process is quite common. The subsequent growth occurs via clonal expansion. A variety of chromosomal subgroups have been found, implying that myomas can be seen as a common phenotype resulting from several different genetic events.

Myomas are found submucosally (beneath the endometrium), intramurally (within the myometrium) and subserosally (projecting out of the serosal compartment of the uterus), but mostly are mixed forms of these 3 different types.

The presence of estrogen receptors in leiomyoma cells has been studied by Tamaya et al. (Acta Obstet Gynecol Scand 1985; 64(4);307-9). They have shown that the ratios of estrogen receptor compared to progesterone and androgen receptor levels were higher in leiomyomas than in the corresponding normal myometrium.

Surgery has long been the main treatment for myomas. Women who have completed childbearing often undergo a hysterectomy, because this eliminates both the symptoms and the chance of recurrence. For women who desire future pregnancies or for other reasons wish to retain the uterus, other options are available. Myomectomy (removal of the myomas with uterine conservation) is widely done. However, the disadvantage of this treatment is the risk of new myoma formation.

Medical therapies that have been proposed to treat myomas include administration of a variety of steroids such as the androgenic steroids danazol or gestrinone, GnRH agonists and progestogens. Both danazol and gestrinone induce amenorrhea, thus controlling myoma-related menorrhagia. Gestrinone also has been reported to cause uterine volume reduction. However, both these drugs have pronounced androgenic side effects like weight gain, acne and hirsutism, which explains the diminishing popularity of these drugs. In addition, these drugs produce a hypoestrogenic milieu causing symptoms such as hot flushes and loss of bone mass.

Gonadotrophin releasing hormone (GnRH) agonists (e.g. nafareline, busereline) give a more complete suppression of ovarian activity by down-regulation of LH and FSH receptors. The GnRH agonists produce a significant reduction in uterine size, however, these drugs

cause serious hypoestrogenic symptoms, such as hot flushes, sweating, headache, vaginal dryness, and loss of bone mass. In addition, the inactivation of the ovaries does not usually result in complete disappearance of myomas. Once the GnRH agonists are discontinued, the size of the uterus increases to pre-treatment volume. Therefore, the GnRH agonists are primarily used temporarily to facilitate surgery. The newly developed GnRH antagonists suppress ovarian endocrine activity even stronger than the GnRH agonists and cause therefore even more serious hypoestrogenism.

The use of progestogens for the treatment of myomas is ineffective for many women. In addition, progestogens cause many side effects and induce hypoestrogenism too.

Because of the induction of a hypoestrogenic status, the aforementioned medical therapies cannot be administered for more than 6 months, in particular not because of the risk of accelerated bone loss resulting in pronounced osteoporosis.

Several studies looked at long term medical therapy of myomas, based on a regimen wherein initially downregulation to a hypogonatropic hypogonadal state is achieved through administration of a GnRH agonist and subsequently an estrogen and a progestogen are administered to sustain the reduction in uterine volume and amenorrhea. A drawback of administering estrogen is that it can cause myoma growth if the dose is too high. The dose that will not give growth of the myomas and counteracts the symptoms of hypoestrogenism varies from person to person. Another drawback of this long term therapy is that it interferes with fertility.

Endometriosis, another well-known gynaecological disorder, affects 10 to 15% of women in the reproductive age. It is a benign disease defined as the presence of viable endometrial gland and stroma cells outside the uterine cavity. It is most frequently found in the pelvic area. In women developing endometriosis, the endometrial cells entering the peritoneal cavity by retrograde menstruation have the capacity to adhere to and invade the peritoneal lining, and are then able to implant and grow. The key question is why endometrial cells adhere and implant in some women and not in others. The implants respond to steroid hormones of the menstrual cycle in a similar way as the endometrium in the uterus. The infiltrating lesions and the blood from these lesions, unable to leave the body, cause inflammation of the surrounding tissue. The most common symptoms of endometriosis are dysmenorrhoea, dyspareunia and (chronic) abdominal pain. The occurrence of these symptoms is not related to the extent of the lesions. Some women with severe endometriosis are asymptomatic, while women with mild endometriosis may have severe pain.

Until now, no non-invasive test is available to diagnose endometriosis. Laparoscopy has to be performed to diagnose the disease. Endometriosis is classified according to the 4 stages set up by the American Fertility Society (AFS). Stage I corresponds to minimal disease while stage IV is severe, depending on the location and the extent of the endometriosis.

Endometriosis is found in up to 50% of the women with infertility. However, currently no causal relation has been proven between mild endometriosis and infertility. Moderate to severe endometriosis can cause tubal damage and adhesions leading to infertility.

Despite extensive research, the cause of endometriosis is still largely unknown. Several theories for the origin of endometriosis have been proposed, although no single hypothesis explains all cases of the disease completely. However, the key event in all these theories is the occurrence of retrograde menstruation.

The aims of treatment of endometriosis are pain relief, resolution of the endometriotic tissue and restoration of fertility (if desired). The two common treatments are surgery or hormonal therapy or a combination of both.

Surgical treatment removes the endometriotic tissue. Initially, the pain relief using this procedure approaches 70-80%. However, the pain returns in many cases due to re-growth of the endometriotic tissue. At present the most permanent way to treat endometriosis is the removal of the ovaries, thus eliminating the production of estrogens and possible other ovarian factors, which regulate the growth and activity of the endometriotic tissue.

The currently available pharmacological treatments of endometriosis are anti-inflammatory and hormonal. In the early stages of endometriosis non-steroidal anti-inflammatory drugs (NSAID's) are often successful in relieving the pelvic pain. Hormonal treatment is given mainly to inhibit the estrogen production by the ovaries. Various drugs are available for suppressing ovarian function as will be explained below.

Endometriosis, like leiomyomas, has been treated with danazol, gestrinone and GnRH agonists. However, the same drawbacks that have been reported above in relation to the use of these drugs in the treatment of myomas have also been observed in the treatment of endometriosis.

Progestogens have been used more frequently in the treatment of endometriosis than for treating leiomyomas, because progestogens inhibit endometrial proliferation. Progestogens are administered in a sufficiently high amount to suppress pituitary release of LH and FSH which in turn causes inhibition of endogenous secretion of estrogen resulting in hypoestrogenic symptoms. Examples of progestogens given for endometriosis are medroxyprogesterone acetate, dydrogesterone and lynestrenol. These drugs are also

associated with side-effects e.g. serious mood changes and breakthrough bleeding. The treatment of endometriosis with progestogens has not received regulatory approval in the United States.

Oral contraceptives, containing both an estrogen and progestogen, are also prescribed for endometriosis. However, this treatment is not optimal, because the stimulatory effect of the estrogenic compound on the endometriotic lesions may not be counteracted effectively enough by the progestogen and because the withdrawal bleeding induced also causes bleeding in endometriotic tissue.

A large percentage of women experience some relief of symptoms while being treated with the hormonal drugs mentioned. However, symptoms remain present and recurrence occurs once administration of the drug is discontinued. None of the aforementioned drugs is suitable for long term treatment of benign gynaecological disorders, because of the severe side-effects which are largely associated with hypoestrogenism. These treatments are therefore in most cases discontinued after a period of 6 months after which recurrence of the symptoms is likely to occur.

It will be evident from the above that there is a great need for a pharmaceutical treatment of uterine leiomyomas and endometriosis, which treatment

(1) can suitably be applied for a much longer period of time than the existing hormonal treatments, preferably until such time that the female treated reaches menopause

(2) is more effective,

(3) causes less side-effects during treatment and/or

(4) has a lower recurrence rate after discontinuation of the therapy.

Everything that has been said above in relation to the treatment of uterine leiomyomas and endometriosis equally applies to other benign gynaecological disorders, notably adenomyosis, functional menorrhagia and metrorrhagia. These benign gynaecological disorders are all estrogen sensitive and are treated in a comparable way as described herein before in relation to uterine leiomyomas and endometriosis. The available pharmaceutical treatments, however, suffer from the same major drawbacks as mentioned above, i.e. they have to be discontinued once the side-effects become more serious than the symptoms to be treated and symptoms reappear after discontinuation of the therapy.

It has also been suggested in the prior art to treat benign gynaecological disorders by administering aromatase inhibitor. US 4,978,658 describes a method of treatment of prevention of an endocrine-dependent condition in a mammal, which comprises administering an effective amount of an aromatase inhibitor. Endocrine-dependent conditions mentioned in

the US-patent include breast cancer, uterine cancer, gynecomastia, precocious puberty, endometriosis and feminizing adrenal tumor. Oral administration is said to be the preferred mode of administration. Like all of the aforementioned methods, oral administration of significant amounts of aromatase inhibitor has the disadvantage that it will inhibit the endogenous production of all estrogens and consequently will lead to hypoestrogenism.

US 6,274,573 describes a method of reducing the recurrence of uterine leiomyoma comprising administering an effective amount of dienogest (a progestogen). It is observed that dienogest may be used in combination with GnRH agonists, GnRH antagonists, aromatase inhibitors and antiestrogens. It is noted that this method relies on the ability of the dienogest to suppress the pituitary release of FSH and LH and that this method will also cause hypoestrogenism.

Thus, it can be concluded that an important shortcoming of all existing medical therapies for the treatment of estrogen sensitive benign gynaecological disorders is that none of them is curative, i.e. they do not lead to disappearance of the myomas, endometriotic and adenomyotic tissue. In addition, they all suffer from side-effects due to hypoestrogenism, which become more pronounced as the duration of the therapy increases.

Consequently there is a need for a long term medical therapy of estrogen sensitive benign gynaecological disorders, particularly for pre- and peri-menopausal females, that does not cause serious side-effects. In addition there is a strong need for a long term medical therapy that will obviate the need for surgical treatments such as hysterectomy and myomectomy.

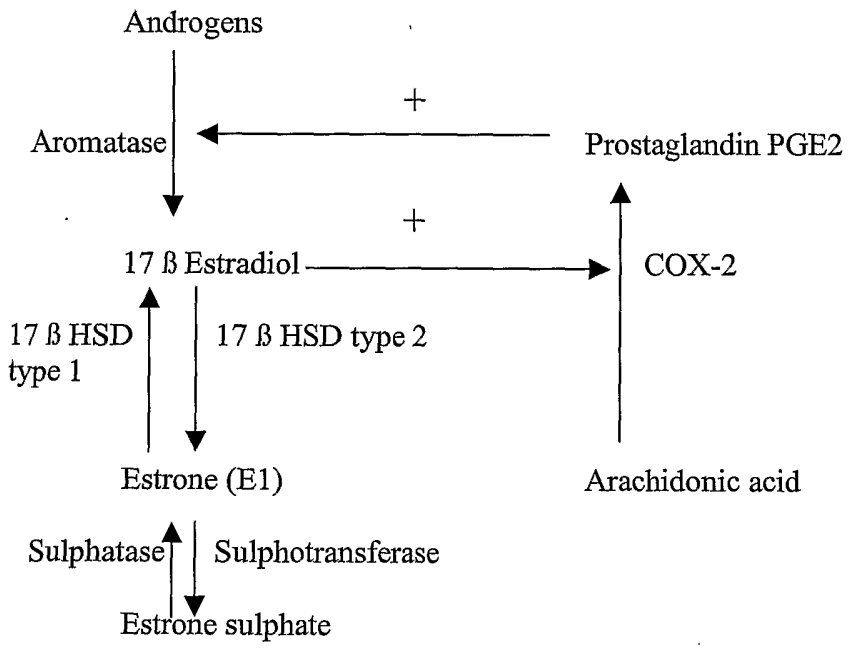
SUMMARY OF THE INVENTION

The present invention relates to a method of treatment that realises the aforementioned objectives, i.e. it can be applied in the treatment of the aforementioned benign gynaecological disorders for a significantly longer period of time than existing medications, as it causes less side-effects enabling long term therapy thereby avoiding the need for surgical procedures.

Applicants have surprisingly found that the aforementioned objectives may be realised by a method of treatment that comprises intravaginal administration to a female mammal of a therapeutically effective dosage of a selective estrogen enzyme modulator (SEEM) selected from the group consisting of aromatase inhibitors, cyclo-oxygenase 2 (COX-2) inhibitors, 17β-hydroxysteroid dehydrogenase type 1 inhibitors and combinations thereof. Although we

do not wish to be bound by theory, it is believed that proliferation of myomas, endometriotic, adenomyotic and endometrial tissue is the result of estrogen induced autostimulation (paracryne), i.e. that these tissues are capable of synthesising estrogens and that these estrogens will bind with the estrogen receptors within the same tissue, thereby triggering (further) proliferation. It was found to be possible to effectively stop this cascade of proliferation by the intravaginal administration of a SEEM. Moreover, it was observed that this may be achieved without serious interference with the body's hormonal balance.

The biosynthetic pathways that are involved in the endogenous production of the most important biogenic estrogen, i.e. 17β-estradiol, may be represented as follows:



As is evident from the above diagram, aromatase and 17β-hydroxysteroid dehydrogenase type 1 are key enzymes in the endogenous production of 17β-estradiol. This is also believed to be true for the production of 17β-estradiol in e.g. myomas or endometriotic tissue. Consequently, the inhibition of aromatase and 17β-hydroxysteroid dehydrogenase type 1 in these tissues will automatically reduce the production of 17β-estradiol, which in turn will impair proliferation in said tissues.

The diagram also shows that prostaglandin PGE2 is capable of stimulating aromatase activity. Consequently, inhibition of cyclo-oxygenase 2 (COX-2), the enzyme responsible for the endogenous production of PGE2 from arachidonic acid, will automatically cause a reduction of aromatase activity and a corresponding decrease in proliferation.

Thus it may be concluded that aromatase inhibitors, cyclo-oxygenase 2 (COX-2) inhibitors as well as 17β-hydroxysteroid dehydrogenase type 1 inhibitors may suitably be used to impair endogenous production of estrogens, particularly the endogenous production of 17β-estradiol, in myomas, endometriotic, adenomyotic and endometrial tissue. Expression of COX-2 has been observed in endometrial tissue and is suspected in adenomyotic tissue, which serves to illustrate that COX-2 is involved in the estrogen induced proliferation of such tissues.

Aromatase is one of the P-450 enzymes. It catalyses the aromatisation of the A ring of the steroid skeleton in the steroid biosynthetic pathway starting from the cleavage of the side chain of cholesterol. To be more precise: aromatase catalyses the conversion of androstenedione to estrone as well as the conversion of testosterone to estradiol. Hence aromatase is a rate limiting enzyme for the biosynthesis of the latter estrogens.

Aromatase inhibitors are substances capable of inhibiting the catalytic activity of aromatase. In the context of the present invention aromatase inhibitors are substances that may be administered to animals, and especially humans, in non-toxic dosages so as to inhibit estrogen biosynthesis. At present a range of aromatase inhibitors is available and includes substances such as aminoglutethimide, anastrozole, exemestane, vorozole, letrozole, fadrozole, rogletimide, atamestane, formestane, liarozole, YM 511, TZA-2237, CGS 16949A and MEN 11066. Aromatase inhibitors primarily find application in methods of treating breast cancer. It has also been suggested that aromatase inhibitors may be used in the treatment of endometriosis. Takayama et al. (Fertility Sterility 1998; 69(4);709-13) successfully treated one case of an unusually aggressive recurrent postmenopausal endometriosis with an aromatase inhibitor. All existing therapies with aromatase inhibitors are based on oral or intramuscular administration.

Cyclooxygenase (COX), also known as prostaglandin G/H synthase, is a membrane-bound enzyme responsible for the oxidation of arachidonic acid to prostaglandins that was first identified over 20 years ago. In the past decade, however, more progress has been made in understanding the role of cyclooxygenase enzymes in various pathophysiological conditions. Two cyclooxygenase isoforms have been identified and are referred to as COX-1 and COX-2. COX-1 enzyme is constitutively expressed and regulates a number of housekeeping functions such as vascular hemostasis and gastroprotection, whereas COX-2 is inducible (i.e., sites of inflammation) by a number of mediators such as growth factors, cytokines and endotoxins.

Nonsteroidal anti-inflammatory drugs (NSAIDs) produce their therapeutic effects through inhibition of COX, the enzyme that makes prostaglandins. Most traditional NSAIDs inhibit both COX-1 and COX-2 isoforms of cyclo-oxygenase. Non-selective inhibition of COX iso-enzyme leads to not only beneficial therapeutic effects but also a number of detrimental effects. Examples of COX-2 selective inhibitors include: celecoxib; deracoxib; valdecoxib; rofecoxib; parecoxib; etoricoxib; meloxicam; etoldolac; lumiracoxib; nimesulide; leflunomide; tilmacoxib and flosulide.

Intravaginal administration of COX-2 inhibitors is mentioned in US 6,086,909 which relates to a method of treating dysmenorrhea. The method described in this US-patent employs intravaginal administration of a pharmaceutical agent selected from the group consisting of a nonsteroidal anti-inflammatory drug, anti-prostaglandin, prostaglandin inhibitor, COX-2 inhibitor, local anesthetic, calcium channel blocker, potassium channel blocker, .beta.-adrenergic agonist, leukotriene blocking agent, smooth muscle inhibitor, vasodilator, and a drug capable of inhibiting dyskinetic muscle contraction.

Examples of 17β-hydroxysteroid dehydrogenase type 1 inhibitors (17 ß-HSD type 1 inhibitors) include: N-butyl, N-methyl, 9-[3'17'beta-(dihydroxy)-1',3',5'(10')-estratien-16 álpha-yl]-7 bromononamide; N-butyl, N-methyl, 7-[3',17'beta-dihydroxy-1',3',5'(10')-estratiene-6' beta-yl]-7-thiaheptanamide.

The particularly good results observed for the intravaginal administration of SEEM are believed to be largely due to the fact that, unlike all regimens that have been practised so far, the present method does not suppress the pituitary release of follicle stimulating hormone (FSH) and luteinising hormone (LH) and therefore does not inhibit ovarian stimulation. The present method counteracts the proliferative effect of endogenous estrogen on myomas, endometriotic, adenomyotic and endometrial tissue in a very effective way by directly and selectively inhibiting the endogenous biosynthesis of estrogens within the aforementioned tissues, thereby preventing stimulation of the estrogen receptors present in these same tissues. It was found that intravaginal administration of SEEM, in comparison to other routes of administration, achieves the desired clinical effect at lower dosage levels and/or without seriously affecting estrogen blood serum levels. Hence the present method may suitably be applied over a prolonged period of time, thereby significantly increasing the chance of achieving complete disappearance of the uterine leiomyomas, endometriotic or adenomyotic tissue. Furthermore, intravaginal administration of SEEM in accordance with the present invention offers the advantage that it has much less impact on the liver than, for instance, oral administration.

DETAILED DESCRIPTION OF THE INVENTION

One aspect of the present invention is concerned with a method of treating a benign gynaecological disorder in a female mammal using a drug delivery vehicle, said benign gynaecological disorders being selected from the group consisting of uterine leiomyomas, endometriosis, adenomyosis, functional menorrhagia and metrorrhagia, the method comprising intravaginal administration of the drug delivery vehicle to the female mammal suffering from the benign gynaecological disorder, said drug delivery vehicle containing a selective estrogen enzyme modulator (SEEM), wherein the method provides the SEEM in a therapeutically effective dosage to prevent or reduce symptoms of said benign gynaecological disorder, said SEEM being selected from the group consisting of aromatase inhibitors, cyclo-oxygenase 2 (COX-2) inhibitors, 17β-hydroxysteroid dehydrogenase type 1 inhibitors and combinations thereof.

The present method also encompasses the prophylactic treatment of the aforementioned benign gynaecological disorders. The term "drug delivery vehicle" as used throughout this document encompasses any pharmaceutical dosage systems suitable for delivering a pharmaceutically active principle to a mammal in such a way that the active principle can exert a pharmaceutical effect on said mammal. Because the present drug delivery vehicle is used in a method of intravaginal administration it should be suitable for vaginal insertion. Examples of drug delivery vehicles suitable for intravaginal use include suppositories, tampons, vaginal rings, tablets, capsules, gels and creams. In a preferred embodiment, said drug delivery vehicle is solid or semi-solid so as to facilitate insertion into the vagina. A preferred example of a solid vehicle is a tablet, capsule, suppository or a vaginal ring. It is noted that the solid drug delivery vehicle does not have to be entirely solid as, for instance, such a vehicle may suitably comprise a solid capsule and a liquid contained within said capsule. In principle any known aromatase inhibitor, COX-2 inhibitor or 17 ß-HSD type 1 inhibitor which is suitable for pharmaceutical application can be used in the present method.

Aromatase inhibitors which may suitably be used in accordance with the invention are aminoglutethimide, anastrozole, exemestane, vorozole, letrozole, fadrozole, rogletimide, atamestane, formestane, liarozole, finrozole, YM 511, TZA-2237, CGS 16949A, MEN 11066, precursors of the aforementioned substances, and mixtures thereof. Preferably the aromatase inhibitor is selected from the group consisting of anastrozole, exemestane, vorozole, letrozole and formestane, precursors of these substances, and mixtures thereof.

COX-2 inhibitors suitable for use in the present method include the following 5 classes of compounds: carbocycles and heterocycles with vicinal aryl moieties, diaryl- or aryl/heteroaryl-ether and -thioether derivatives, cis-Stilbene derivatives, diaryl and aryl/heteroaryl ketones and compounds with antioxidative moieties. Specific examples of COX-2 inhibitors that may be employed in accordance with the present invention can be found in Dannhardt et al. (Curr Med Chem 2000 Nov; 7(11): 1101-12), which is incorporated herein by reference.

Preferably the COX-2 inhibitors used in the present method are compounds which are at least 5-fold selective for COX-2 over COX-1 in terms of IC 80 values in the WHMA/COX-1 determination (Warner TD et al. PNAS 1999; 96(13): 7563). Examples of suitable COX-2 inhibitors that are currently available include: celecoxib; deracoxib; valdecoxib; rofecoxib; etoricoxib; parecoxib; meloxicam; etoldolac; lumiracoxib; nimesulide; leflunomide; tilmacoxib; flosulide; diisopropyl fluorophosphates; L745,337; SC-58125; L743337; SC-236; BMS-347070; GW-406381 and E-6087.

Preferred 17 ß-HSD type 1 inhibitors for use in the present method are selected from the group consisting of bromoacetoxy derivatives of estradiol, bromoacetoxy derivatives of estrone, bromoacetoxy derivatives of 4-androstenedione, bromoacetoxy derivatives of progesterone, bromoacetamido derivatives of estrone, arylazido-beta-alanine derivatives of estradiol or estrone, 16-methylene-estradiol, 17-beta-propynyl-substituted progestin analogs, acetylenic or trifluoromethylacetylenic 14,15-secoestradiols, 16 alpha-(halogenoalkyl) estradiol derivatives, 6 beta-(thiaheptanamide) derivatives of estradiol (e.g N-butyl, N-methyl, 7-[3',17'beta-dihydroxy-1',3',5'(10')-estratiene-6' beta-yl]-7-thiaheptanamide), N-butyl, N-methyl, 9-[3'17'beta-(dihydroxy)-1',3',5'(10')-estratien-16 álpha-yl]-7 bromononamide and mixtures thereof.

The main function of the SEEM as used in the present method is to suppress the biosynthesis of biogenic estrogens, notably estradiol, in the target tissues. Thus the administration of the SEEM will lead to a reduction in estrogen-induced proliferation of uterine leiomyomas, endometriotic lesions, adenomyomas and endometrial tissue.

The present method may successfully be applied to female mammals. Preferably these mammals include humans, cattle and pets. Most preferably the female mammal is a human female.

The present method provides the SEEM in a therapeutically effective dosage to inhibit growth of myomas, endometriotic, adenomyotic or endometrial tissue. By inhibition of the growth of these tissues is meant that existing myomas, endometriotic, adenomyotic or

endometrial tissue do not increase in volume as a result of proliferation and that no new tissues of these sorts are formed. In a particularly preferred embodiment of the present invention the SEEM is provided in a therapeutically effective dosage to achieve atrophy of the aforementioned tissues. Most preferably the method provides said SEEM in a therapeutically effective dosage to achieve full elimination of these tissues.

As mentioned herein before, the present method offers the advantage that due to the local (intravaginal) administration it selectively inhibits the biosynthesis of estrogens, especially 17β-estradiol in myomas, endometriotic, adenomyotic or endometrial tissue. In contrast, well known methods of treating benign estrogen sensitive gynaecological disorders, completely suppress the endogenous production of estrogen throughout the female's body, giving rise to serious side-effects, particularly after prolonged treatment. Consequently, in a very preferred embodiment, the present method is carried out in such a fashion that it does not inhibit estrogen synthesis by the ovaries or elsewhere in the body due to the low or absent systemic exposure to the SEEM. It will be evident that the present method preferably does not employ active principles that may suppress the pituitary release of FSH or LH. More preferably, the drug delivery vehicle employed in the present method contains virtually no progestogen or GnRH agonist. Also it is preferred not to co-administer either of these 2 active principles in combination with the present SEEM containing drug delivery vehicle.

It was found that intravaginal administration of a SEEM in comparison to other routes of administration, achieves the desired clinical effect at relatively low dosage levels (expressed in absorbed amount per kg of bodyweight) and without seriously affecting overall estrogen blood serum levels. Hence the present method may suitably be applied over a prolonged period of time, thereby significantly increasing the chance of achieving complete disappearance of the leiomyomas, endometriosis and/or adenomyosis.

In order for the present method to be effective it is desirable that the intravaginal administration of the SEEM occurs in an amount which is therapeutically effective to inhibit the endogenous synthesis of 17β-estradiol in the myomas, endometriotic, adenomyotic or endometrial tissue.

The intravaginally administered dosage of the SEEM will usually exceed 10 μg/day. Preferably said amount will be in the range of 20 μg/day to 250 mg/day, more preferably in the range of 50 μg/day to 100 mg/day. In a preferred embodiment of the invention, the present method comprises intravaginal administration of the SEEM in an amount which is equivalent to a daily intravaginal dosage of 100 μg to 250 mg exemestane, preferably of 150 μg to 100 mg exemestane and more preferably of 250 μg to 25 mg exemestane. In a particularly

preferred embodiment of the invention the SEEM is administered in an amount which is equivalent to a daily intravaginal dosage of less than 16 mg, even more preferably of less than 8 mg exemestane. The phrase "equivalent to a daily dosage" should not be interpreted restrictedly. For instance, the above mentioned requirement that the administration of the present drug delivery vehicle is to provide the equivalent of a daily dosage of 100 μg to 250 mg exemestane, encompasses a protocol wherein exemestane is administered once a week, provided the weekly dosage is between 700 μg and 1750 mg, i.e. such that the average daily dose is between 100 μg and 250 mg. The recommended dosages may alternatively be expressed in equivalent daily intravaginal dosages of rofecoxib (a COX-2 inhibitor) in which case the latter dosages are identical to those recited for the aromatase inhibitor exemestane.

In a particularly preferred embodiment of the present invention the SEEM is selected from the group consisting of aromatase inhibitors, COX-2 inhibitors and combinations thereof. Most preferably one or more aromatase inhibitors are employed as the SEEM in the present method.

In order to achieve very effective inhibition of endogenous estrogen formation it is advisable to use a combination of SEEMs that each inhibit different pathways of estrogen biosynthesis. Preferably a combination comprising an aromatase inhibitor and a COX-2 inhibitor and/or a 17 ß-HSD type 1 inhibitor is employed. Most preferably a combination comprising an aromatase inhibitor and a COX-2 inhibitor is used.

The efficacy of the present method may also be enhanced by the co-administration of a sulphatase inhibitor. As can be seen from the biosynthesis diagram that was presented before, the endogenously produced estrogen estrone may be enzymatically converted to 17β-estradiol by 17β-hydroxysteroid dehydrogenase type 1. Through an alternative pathway, estrone may also be converted to estrone sulphate, which is essentially inactive. Estrone sulphate can be reconverted into estrone by sulphatase. Inhibition of the latter enzyme will result in a general lowering of blood serum estrone levels and accumulation of estrone sulphate. As will be evident from the biosynthesis diagram, such a lowering of the estrone level will be accompanied by a similar lowering of the 17β-estradiol level. Consequently, the co-administration of a sulphatase inhibitor will improve the efficacy of the present method as it enhances the action of the SEEM. Preferably the sulphatase inhibitor is co-administered intravaginally as such a mode of administration allows the inhibitor to exert a localised effect on the tissue to be treated rather than a systemic effect throughout the body.

Examples of sulphatase inhibitors include: estrone-3-O-sulfamate (EMATE), 4-methyl-coumarin-7-O-sulfamate (COUMATE), 665-COUMATE, 666-COUMATE, 667-

COUMATE, 668-COUMATE, 669-COUMATE, 4-sulfamated phenyl ketone derivatives, 4-sulfamated phenyl alkyl ketone derivatives, 4'-O-sulfamoyl-4-biphenyl derivatives.

An important advantage of the present method resides in the fact that, unlike existing methods, it may be employed for prolonged periods of time, without causing serious side-effects. Hence in a preferred embodiment the present method comprises continuous intravaginal administration of the SEEM for a period of at least 3 months, preferably at least 6 months. It is noted that with the present method usually a treatment period of at least 3-6 months is necessary to obtain significant atrophy or complete disappearance of the target tissue.

The term "continuous" when used in relation to the administration of one or more active principles, means that said one or more active principles are administered at relatively regular intervals, with no (therapeutically) significant interruptions. Naturally, minor interruptions may occur that do not affect the overall effectiveness of the present method, and indeed such aberrations are encompassed by the present invention. In a preferred embodiment, and more arithmetically, an administration regimen is deemed to be continuous if the longest interval between 2 subsequent administrations is not more than 3.5 times as long as the average interval. Even more preferably said longest interval is not more than 2.5 times as long as the average interval.

The drug delivery vehicle used in the present method is preferably administered intravaginally at intervals of between 12 hours and 90 days. More preferably said vehicle is administered between once a day or once a month. In a particularly preferred embodiment of the invention, the method employs between once weekly and once monthly intravaginal administration of the drug delivery vehicle. In case the administration intervals exceed one day, it can be advantageous to use a slow release drug delivery vehicle, particularly a vehicle that, following intravaginal administration, is capable of releasing the preferred daily dosage amounts during a period of at least 5, or more preferably at least 10 days, without intermediate replenishment.

In another preferred embodiment of the invention the present method of treating the benign gynaecological disorders comprises co-administration of an estrogen in a therapeutically effective amount to reduce possible symptoms of hypoestrogenism resulting from the intravaginal administration of the SEEM. As mentioned herein before, the present method offers the advantage that, due to the non-systemic and relatively low intravaginal dosage of the SEEM, it will produce significantly less symptoms of hypoestrogenism than known methods for treating estrogen sensitive gynaecological disorders. However, in

particular during prolonged treatment, certain symptoms of hypoestrogenism, such as hot flushes, may become manifest. These symptoms may suitably be suppressed by co-administering estrogen in a therapeutically effective dosage to compensate for the estrogen deficiency symptoms occurring at other parts of the body than the pelvis and the uterus, resulting from the intravaginal administration of the SEEM. In order to minimise any adverse impact of the co-administered estrogen on the desired effect of the intravaginally administered SEEM, it is preferred to use a mode of administration for applying the estrogen which is different from intravaginal or intra-uterine administration.

We have unexpectedly found that, in particular if the estrogen is administered systemically (e.g. orally), the blood serum estrogen level may be restored to its usual level, without the administered estrogen having a significant effect on the proliferation of the leiomyomas, endometriotic and/or adenomyotic tissue. In a preferred embodiment of the present method estrogen is co-administered with the SEEM so as to maintain the estrogen blood serum level of the female at a level which is equivalent to at least 30 pg 17ß-estradiol/ml. Most preferably the 17ß-estradiol blood serum level of the female is maintained at a level of at least 30 pg/ml.

The estrogen used in the present method is preferably selected from the group consisting of ethinyl estradiol, mestranol, quinestranol, estradiol, estrone, estran, estriol, conjugated equine estrogens, precursors capable of liberating such an estrogen when used in the present method and mixtures thereof. In a preferred embodiment of the method of the invention the estrogen is selected from the group consisting of ethinyl estradiol, estradiol, precursors of these estrogens and mixtures thereof, and administered in an amount equivalent to a daily oral dose of 1-40 μg ethinyl estradiol (e.g. 0.2-5 mg 17β-estradiol) and more preferably in an amount equivalent to 3-30 μg ethinyl estradiol.

As will be readily understood by those working in the field, the amount of SEEM or estrogen that is effective to achieve the desired results may be determined empirically with respect to any given SEEM or estrogen and for any given mammal. The effective dose ranges, as well as being compound specific, may also depend upon patient characteristics, such as age and weight.

In a particularly preferred embodiment of the invention, the method comprises the intravaginal co-administration of an anti-estrogen in an amount effective to prevent the interaction between (endogenous) estrogens, especially 17 β-estradiol, and estrogen receptors in the myomas, endometriotic, adenomyotic or endometrial tissue.

Anti-estrogens are substances which exhibit affinity for the mammalian estrogen receptors without triggering all of the responses that are characteristic of the interaction between estrogens and the same receptors. Thus, when administered in sufficiently high dosage, anti-estrogens will bind in appreciable amounts to estrogen receptors, thereby reducing the estrogen-receptor interaction. Consequently anti-estrogens can suitably be used to reduce or inhibit the impact of estrogens, hence the term "anti-estrogens". The term anti-estrogen as used throughout this document encompasses both anti-estrogens that trigger no estrogen receptor response at all ('true' antagonists) as well as anti-estrogens that are capable of triggering a selective anti-estrogen receptor response. An example of anti-estrogens capable of triggering a selective estrogen receptor response are so called selective estrogen receptor modulators (SERM's). Examples of 'true' anti-estrogens that may be used in the present method include ICI 164384, ICI 182780, ZM 189154, EM-800, RU 58668, precursors of these anti-estrogens, and mixtures thereof.

In addition, anti-estrogens that exert SERM-like activity as well as their precursors may suitably be used in the present method. Such SERM-like anti-estrogens can suitably be selected from the group consisting of tamoxifen, raloxifene, toremifene, idoxifene, droloxifene, nafoxidine, trioxifene, MER 25, EM-652, clomiphene, cyclophenil, lasofoxifene, arzoxifene, levormeloxifene, zindoxifene, LY 117018, LY 326315, ZK 119010, LY 357489, GW 5638, GW 7604, TSE-424, FC1271a and mixtures thereof. It has been reported (Osteoporosis Conference Scrip No. 1812/13 Apr. 16/20, 1993, p. 29) that raloxifene (6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy) benzoyl] benzo[b] thiophene) mimics the favourable action of estrogen on bone and lipids but, unlike estrogen, has minimal uterine stimulatory effect. (Breast Cancer Res. Treat. 10(1). 1987 p 31-36 Jordan, V. C. et al.).

Preferably the anti-estrogen used in accordance with the invention is selected from the group consisting of ICI 164384, ICI 182789, raloxifene, tamoxifen, precursors of these substances, and mixtures thereof. Most preferably the anti-estrogen is selected from the group consisting of ICI 164384, ICI 182789, precursors of these substances and mixtures thereof. In accordance with the invention, the anti-estrogen is suitably co-administered in an amount equivalent to a daily dosage of less than 600 mg raloxifene, preferably of more than 250 μg raloxifene and more preferably in an amount equivalent to a daily dosage of 600 μg to 60 mg raloxifene. In a particularly preferred embodiment the anti-estrogen is administered in an amount which is equivalent to less than 30 mg, more preferably even less than 20 mg raloxifene.

The combined administration of anti-estrogen and SEEM offers the advantage that estrogen induced proliferation of myomas, endometriotic, adenomyotic or endometrial tissue can be suppressed in an extremely effective dual manner. The combined intravaginal administration of anti-estrogen and SEEM ensures that on the one hand endogenous biosynthesis of estrogens in the target tissues is reduced to almost zero, whilst the anti-estrogen effectively prevents that any remaining local or circulating estradiol can interact with estrogen receptors in the aforementioned tissues.

Another embodiment of the present method comprises co-administration of an androgen. The androgen enhances the action of the SEEM, in particular the SEEM's ability to suppress growth, proliferation and viability of endometriotic tissue, adenomyomas, fibroids and endometrial tissue and/or suppresses the undesirable side-effects of said SEEM, particularly those side-effects associated with hypo-estrogenism.

Because androgens are precursors of estrogens, one would expect the administration of androgen to enhance the growth, proliferation and viability of the endometriotic tissue, adenomyomas, fibroids and endometrial tissue, and thus cause a worsening of the disease. However, surprisingly the androgen component used in accordance with the present invention has an enhancing effect on the anti-proliferative action of the SEEM.

The androgen may exert this effect through activation of androgen receptors. It is known that androgen receptors are present in endometriotic and endometrial tissue, as well as in adenomyosis. Horie et al., "Immunohistochemical localisation of androgen receptor in the human endometrium, decidua, placenta and pathological conditions of the endometrium", Hum. Repr. vol. 7, nr. 10 (1992), pp. 1461-1466 report that although the proliferation and differentiation of endometrium are mediated mainly by estrogen and progesterone receptors, the androgen receptor may play a role in modulating these changes. As yet, however, there is no scientific proof that indeed these androgen receptors play a role in the proliferation of endometriotic tissue, adenomyosis, fibroids and endometrial tissue.

The term "androgen" as used throughout this document relates to steroids that display androgen-like activity. The androgens used in the present method preferably are administered in a dosage where they exert the desired effect, but do not give rise to significant androgenic side-effects such as acne and hirsutism. Preferably the androgen is administered in a dose which leads to an increase in blood serum androgen level of no more than 5 nmole total testosterone equivalent per litre, preferably less than 3 nmole total testosterone equivalent per litre and most preferably less than 1.5 nmole total testosterone equivalent per litre. The total testosterone present in the serum includes both free testosterone and bound testosterone.

The androgen used in the present method is preferably selected from the group consisting of dehydroepiandrosterone (DHEA); DHEA-sulphate (DHEAS); testosterone; testosterone esters such as testosterone undecanoate, testosterone propionate, testosterone phenylpropionate, testosterone isohexanoate, testosterone enantate, testosterone bucanate, testosterone decanoate, testosterone buciclate; danazol; gestrinone; methyltestosterone; mesterolon; stanozolol; androstenedione; dihydrotestosterone; androstanediol; metenolon; fluoxymesterone; oxymesterone; methandrostenolol; MENT, precursors capable of liberating these androgens when used in the present method and mixtures thereof. Most preferably the androgen is selected from the group consisting of DHEA, pharmaceutically acceptable testosterone esters such as testosterone undecanoate, danazol, gestrinone, androstenedione, precursors capable of liberating these androgens when used in the present method and mixtures thereof. Preferably the testosterone esters employed in the present method comprise an acyl group which comprises at least 6, more preferably from 8-20 and preferably 9-13 carbon atoms. Most preferably the androgen used in the present method is DHEA and/or testosterone undecanoate. These androgens offer the advantage that they can effectively be used in oral dosage units.

In a preferred embodiment the androgen is provided in an amount equivalent to a daily oral dosage of 5 to 250 mg DHEA, which is equivalent to a daily oral dosage of 1 to 50 mg testosterone undecanoate. More preferably the androgen is provided in an amount equivalent to a daily oral dosage of 20 to 100 mg DHEA, most preferably in an amount equivalent to a daily oral dosage of 40 to 60 mg DHEA. The phrase "equivalent to a daily dosage" should not be interpreted restrictedly. For instance, the above mentioned requirement that the administration of the present medicament is to provide the equivalent of a daily dosage of 5 to 250 mg DHEA, encompasses a protocol wherein DHEA is administered once a week, provided the weekly dosage is between 35 and 1750 mg, i.e. such that the average daily dose is between 5 and 250 mg DHEA.

It is noted that, for instance, DHEA, testosterone undecanoate and androstenedione are precursors of testosterone and that said precursors *per se* exhibit virtually no affinity for the androgen receptors in the female body. The effectiveness of androgens within the method of the invention is determined by their functionally active form, which may well be different from the form in which they are administered.

In order to obtain the desired impact from the present method it is advisable to administer the medicament at a dosage sufficient to maintain serum androgen concentration of the female mammal within a (physiological) range which is equivalent to between 0.5 and

5.0, preferably to between 0.7 and 4.0, most preferably between 1.0 and 3.0 nanomoles total testosterone per litre. Again, these testosterone concentrations include both free and bound testosterone.

In a particularly preferred embodiment of the invention, the androgen is administered in a systemic fashion. Most preferably the androgen is administered orally. In a particularly preferred embodiment, the present method comprises the combined systemic co-administration of an androgen and an estrogen.

In yet another preferred embodiment the present method comprises co-administration of an anti-progestogen in an effective amount to boost the atrophic effect of the SEEM on the leiomyomas, endometriotic, adenomyotic and endometrial tissue. Although applicants do not wish to be bound by theory it is believed that these tissues, next to estrogen receptors, also express progestogen receptors. Anti-progestogens have been shown to inhibit endometrial proliferation. Thus the combined use of a SEEM and an anti-progestogen is very effective in suppressing such proliferation, but more importantly also in achieving atrophy of the target tissues. In a particularly preferred embodiment also the anti-progestogen is administered intravaginally. Also in case of anti-progestogen the intravaginal administration offers the advantage that, in comparison to systemic administration, the same local clinical effects, with less pronounced side-effects, are achieved at lower systemic blood levels of the anti-progestogen.

The anti-progestogen used in the present method can be a progesterone receptor antagonist or a pharmaceutically suitable agent that counteracts the normal biological activity of progesterone. Examples of anti-progestogens which can be employed in this invention are RU 486 (mifepristone, Roussel Uclaf, Paris; U.S. Pat. No. 4,386,085); Org 31710 [(6.alpha.,11.beta.,17.beta.)-11-(4-NMe.sub.2 -phenyl)-6-Me-4',5'-dihydrospiro[oestra-4,9-diene-17,2(3'H)-furan]-3-one]; Org 33628[(11.beta.,17.alpha.)-(4-acetylphenyl)- 17,23-epoxy-19,24-dinorchola-4,9,20-trien-3-one]; onapristone (Schering Ag, Berlin; U.S. Pat. No. 4,780,461) and the steroids described in the following patents and patent applications: U.S. Pat. No. 4,609,651, especially the compound lilopristone (11β-(4-dimethylaminophenyl)-17β-hydroxy-17α-(3-hydroxy-prop-1-(Z)-enzyl-4,9(10) estradien-3-one); U.S. application Ser. No. 06/827,050, especially the compounds 11β-(4-acetylphenyl)-17β-hydroxy-17α-(1-propinyl)-4,9-estradien-3-one and 11β-(4-acetylphenyl)-17β-hydroxy-17α-(3-hydroxy-1(2)-propenyl)-4,9-estradien-3-one; U.S. application Ser. No. 07/283,632; published European patent application EP-A 04042831; published PCT application WO 91/14704; and other anti-

progestogens, e.g., U.S. Pat. No. 4,891,368. Most preferably the anti-progestogen used in the present method is mifepristone and/or a precursor thereof.

In accordance with the present invention, the anti-progestogen is suitably administered in a daily amount of at least 10 μg. More preferably the minimum daily dosage is equivalent to an intravaginal daily dosage of at least 200 μg, most preferably at least 500 μg mifepristone. The maximum daily dosage of anti-progestogen is preferably equivalent to an intravaginal daily dosage of less than 500 mg mifepristone, more preferably of less than 50 mg mifepristone and most preferably of less than 25 mg mifepristone.

The present method is particularly effective when used in the treatment of uterine leiomyomas, endometriosis or adenomyosis as the main symptoms of these disorders are directly related to endometrial proliferation. Best results are obtained when the present method is used in the treatment of uterine leiomyomas, adenomyosis or rectovaginal endometriosis.

Throughout this document by precursors of an active ingredient are meant components capable of liberating the active ingredient when used in the present method after intravaginal and/or, in the case of estrogen, following oral administration, e.g. as a result of metabolic conversion of the precursor substance.

It is to be understood that the present invention not only encompasses the use of the active principles specifically mentioned in this application, but also the use of metabolites of these components that display comparable functionality. In this context it is noted that, for instance, estriol is a metabolite of 17beta-estradiol.

Because the incidence of the aforementioned benign gynaecological disorders drops sharply after females have reached menopause, the present method is particularly useful when used in the treatment of pre- or peri-menopausal females. Most preferably the present method is used to treat premenopausal females.

Another aspect of the invention is concerned with a drug delivery vehicle for intravaginal use, comprising at least 10 μg of a SEEM selected from the group consisting of aromatase inhibitors, 17β-hydroxysteroid dehydrogenase type 1 inhibitors and combinations thereof; and pharmaceutically acceptable excipient. Preferably the amount of SEEM exceeds 20 μg, more preferably said amount exceeds 100 μg. Usually the amount of SEEM will not exceed 600 mg, preferably it will not exceed 400 mg, more preferably it will not exceed 200 mg. Most preferably the drug delivery device contains SEEM in an amount equivalent to at least 250 μg exemestane. The drug delivery vehicle according to the invention may be a

tablet, capsule, gel, cream, film, suppository, tampon, pessary, vaginal sponge, lotion, foam, ointment, paste, solution or a vaginal ring.

In a preferred embodiment the drug delivery vehicle additionally contains anti-estrogen in an amount exceeding 50 μg, more preferably in an amount exceeding 100 μg. Usually the amount of anti-estogen will not exceed 600 mg, preferably it will not exceed 400 mg, more preferably it will not exceed 200 mg. Most preferably the drug delivery vehicle contains anti-estrogen in an amount equivalent to at least 600 μg raloxifene.

Other pharmaceutically functional components that may advantageously be incorporated in the present drug delivery vehicle include COX-2 inhibitors and/or sulphatase inhibitors. Preferably COX-2 inhibitor or sulphatase inhibitor is incorporated in an amount of at least 10 μg. More preferably the COX-2 inhibitor is present in an amount equivalent to at least 100 μg rofecoxib. The amount of COX-2 inhibitor will normally not exceed the equivalent of 250 mg rofecoxib.In yet another preferred embodiment the drug delivery vehicle additionally contains at least 10 μg of anti-progestogen. Preferably the delivery vehicle contains anti-progestogen in an amount equivalent to at least 200 μg, more preferably at least 500 μg mifepristone. Usually the amount of anti-progestogen will not exceed 500 mg, preferably it will not exceed 300 mg, more preferably it will not exceed 200 mg.

The vaginal suppository may suitably be based on a hard fat, preferably a hard fat having a hydroxy value not exceeding 50. The term `hard fat` means a mixture of glycerides whose constituent fatty acids are straight-chain saturated fatty acids of 8 to 18 carbon atoms, and examples of such hard fat are listed on Martindale The Extra Pharmacopeia, 28ed., p. 1067, London, The Pharmaceutical Press, 1982). The vaginal suppositories according to the present invention may be manufactured by melting the hard fat adding the pharmaceutically active principles, mixing them thoroughly, pouring the composition into suppository moulds in predetermined uniform quantities and cooling them.

In another embodiment, the invention provides a tampon device for delivering the SEEM to the vaginal epithelium, said tampon comprising an absorbent material which has been soaked with a pharmaceutically acceptable solution of the aromatase inhibitor. A retrieval string or tape may be connected to the tampon device so as to facilitate easy removal. When administered the tampon contacts the vaginal epithelium for delivery of the agent.

In yet another embodiment the delivery vehicle may be a vaginal ring. Vaginal rings are torus shaped devices designed to deliver a relatively constant dose of drug to the vagina usually over a period of weeks to months. Typically, they are made of a poly EVA elastomer and contain a drug released by diffusion though the elastomer. The most common commercial

applications have been to deliver low doses of steroids for post-menopausal vaginal conditions. They have also been under development for use in contraception and hormone replacement therapy. Vaginal rings have also been used to administer spermicides, as well as a variety of locally or systematically active medicaments.

The use of a vaginal ring to deliver drugs requires a ring design that regulates the release rate so as to provide the user with the appropriate daily dose. Among the important factors governing release are the solubility of the drug in the ring elastomer, the surface area of the drug reservoir, the distance the drug must diffuse through the ring body to reach its surface and the molecular weight of the drug.

If very high release rates are desired, they can be attained by a drug load at the ring surface as is characteristic of the homogeneous matrix ring design. This design, however, suffers from rapidly declining release rates as the distance the drug must travel to reach the ring surface increases as the drug load near the surface is depleted. If moderately high release rates are needed to provide the appropriate dose, a design which modulates the release rate by imposing a layer of drug-free elastomer between the drug reservoir and the ring exterior is appropriate. If an even lower release rate is desired, the drug may be confined to a small diameter at the centre of the ring ("core ring"). Numerous types of vaginal rings have been described in the patent and non-patent literature alike.

Yet another aspect of the present invention relates to a pharmaceutical kit comprising a drug delivery vehicle as defined herein before and a plurality of oral dosage units comprising estrogen in an amount equivalent to at least 1 μg ethinyl estradiol and/or androgen in an amount equivalent to 5-250 mg DHEA. As explained herein before the combination of intravaginal administration of SEEM and oral administration of estrogen and/or androgen was found to be particularly effective in treating leiomyomas, endometriotic and/or adenomyotic tissue with minimum side-effects. Preferably the estrogen and/or androgen containing medicament is designed for once daily oral administration. Accordingly, the preferred amount of estrogen and/or androgen included in the oral dosage units corresponds to the daily dosages that have been advocated herein before.

The dosage units in the aforementioned kit may advantageously contain an anti-estrogen and/or an anti-progestogen. Preferably the anti-estrogen is incorporated in the intravaginal drug delivery device in an amount of at least 10 μg. The anti-progestogen is also suitably incorporated in the intravaginal drug delivery device, typically in an amount of at least 10 μg.

The invention is further illustrated by means of the following examples.

EXAMPLES

Example 1

A clinical efficacy study is conducted in 10 women with uterine fibroids, who have to undergo a myomectomy or a hysterectomy. Each participant receives a daily dosage of 25 mg exemestane intravaginally. Before the start of the study the number and size of the fibroids is assessed by ultrasonography for each participant. This procedure is repeated every week after the start of the study until the female undergoes myomectomy or hysterectomy. During the period of study participants are recording symptoms of hypoestrogenism in a diary. After 8-10 weeks of vaginally administered exemestane, the size of the fibroids is reduced in all participants. Reductions in total fibroids volume of up to 75% are observed. Some women experience symptoms of hypoestrogenism.

Example 2

Example 1 is repeated. However, instead of exemestane the participants receive a daily intravaginal dosage of 25 mg rofecoxib. The participants show significant fibroid atrophy after 8-10 weeks of treatment.

Example 3

A clinical study is conducted in 10 women with stage 3 or 4 rectovaginal endometriosis, complaining from severe dyspareunia and/or low pelvic pain and/or painful defecation. The women receive a daily intravaginal dosage of 25 mg exemestane for 8-10 weeks. At the start of the study the size of the endometriotic lesions is assessed by ultrasonography and rectovaginal examination by palpation.

Every week the women fill out a questionnaire assessing the level and occurrence of dyspareunia, low pelvic pain and painful defecation. In addition, the study participants are recording symptoms of hypoestrogenism in a diary. Every week during the 8-10 week study period an ultrasonography and rectovaginal examination is performed or when treatment is discontinued.

Results show that all women have a reduction of pain after 8-10 weeks of treatment. Within this period, the size of the endometriotic lesions is reduced in all participants. Some women experience symptoms of hypoestrogenism.

Example 4

Example 3 is repeated. The participants additionally receive a intravaginal dosage of 25 mg rofecoxib. The participants receiving the combination of vaginal exemestane and rofecoxib show a larger reduction of pain and of the size of the endometriotic lesions during the treatment than the females described in example 3, who only receive exemestane and the females described in example 2, who only receive rofecoxib.

Example 5

Example 1 is repeated. The participants additionally receive a daily oral dosage of 1 mg 17-β estradiol. The participants receiving the combination of vaginal exemestane and oral estrogen show significant fibroid atrophy during the treatment, show no endometrial growth in the uterus and record less symptoms of hypoestrogenism than the females described in example 1, who only receive exemestane.

Example 6

Example 3 is repeated. The participants additionally receive a daily oral dosage of 1 mg 17-β estradiol. The participants receiving the combination of vaginal exemestane and oral estrogen show significant reduction of pain and of the size of the endometriotic lesions during the treatment and record less symptoms of hypoestrogenism than the females described in example 1, who only receive exemestane.

Example 7

Example 1 is repeated. The participants who receive exemestane additionally receive a daily intravaginal dosage of 30 mg raloxifene. The participants receiving the combination of exemestane and raloxifene show a larger reduction of fibroid size than the participants of example 1 who receive only exemestane.

Example 8

A clinical study is conducted in 20 women with stage 3 or 4 endometriosis, complaining from severe dysmenorrhoea and/or abdominal pain. Ten women are randomised to a treatment group receiving a daily intravaginal dosage of 25 mg exemestane. The other ten women receive a daily intravaginal dosage of 25 mg exemestane together with a oral dosage of 50 mg dehydroepiandrosterone (DHEA). Both groups are treated for 6 months.

Before the start of the study a laparoscopy is performed. Every 4 weeks the women fill out a questionnaire assessing the level and occurrence of abdominal pain. In addition, the study participants are recording symptoms of hypoestrogenism in a diary. A second laparoscopy is performed after 6 months of treatment or when treatment is discontinued. Results show that all women have a reduction of pain after 6 months of treatment. Within this period, the endometriotic lesions are reduced in all participants receiving exemestane with or without DHEA. The women receiving DHEA report a larger reduction in pain and also show a more pronounced reduction in size of the endometriotic lesions compared to the women not receiving DHEA. A few women experience symptoms of hypoestrogenism. A trend can be seen that the women receiving DHEA experience less subjective side-effects than the women not receiving DHEA.

Example 9

Example 1 is repeated with the exception that the participants who receive exemestane additionally receive a daily intravaginal dosage of 10 mg mifepristone. The participants receiving the combination of exemestane and mifepristone show a larger reduction of fibroid size than the participant of example 1 who receive only exemestane.

CLAIMS

1. Use of a selective estrogen enzyme modulator (SEEM) in the manufacture of a drug delivery vehicle for use in a method of treating or preventing a benign gynaecological disorder in a mammalian female, said benign gynaecological disorder being selected from the group consisting of uterine leiomyomas, endometriosis, adenomyosis, functional menorrhagia and metrorrhagia, wherein the method comprises the intravaginal administration of the SEEM to the female suffering from the benign gynaecological disorder in a therapeutically effective dosage to prevent or reduce the symptoms of said benign gynaecological disorder, said SEEM being selected from the group consisting of aromatase inhibitors, cyclo-oxygenase 2 (COX-2) inhibitors, 17β-hydroxysteroid dehydrogenase type 1 inhibitors and combinations thereof.

2. Use according to claim 1, wherein the method comprises the intravaginal administration of the SEEM in a sufficient amount to inhibit growth or to achieve atrophy of the uterine leiomyomas, endometriotic, adenomyotic or endometrial tissue.

3. Use according to claim 1 or 2, wherein the method does not inhibit (ovarian) estrogen synthesis.

4. Use according to any one of claims 1-3, wherein the method comprises intravaginal administration of the SEEM in an amount which is equivalent to a daily intravaginal dosage of 100 μg to 250 mg exemestane, preferably of 150 μg to 100 mg exemestane and more preferably of 250 μg to 25 mg exemestane.

5. Use according to any one of claims 1-4, wherein the SEEM comprises one ore more aromatase inhibitors.

6. Use according to claim 5, wherein the one or more aromatase inhibitors are selected from the group consisting of aminoglutethimide, anastrozole, exemestane, vorozole, letrozole, fadrozole, rogletimide, atamestane, formestane, liarozole, YM 511, TZA-2237, CGS 16949A, MEN 11066 and precursors of the aforementioned substances.

7. Use according to any one of claims 1-4, wherein the SEEM comprises one or more COX-2 inhibitors.

8. Use according to claim 7, wherein the COX-2 inhibitors are selected from the group consisting of celecoxib; deracoxib; valdecoxib; rofecoxib; etoricoxib; parecoxib; meloxicam; etoldolac; lumiracoxib; nimesulide; leflunomide, flosulide; leflunomide; tilmacoxib; diisopropyl fluorophosphates; L745,337; SC-58125; L743337; SC-236, BMS-347070; GW-406381 and E-6087; precursors of these COX-2 inhibitors and combination of these inhibitors and/or precursors.

9. Use according to any one of claims 1-8, wherein the method comprises co-administration of estrogen in a therapeutically effective amount to reduce symptoms of hypoestrogenism resulting from the administration of the SEEM.

10. Use according to any one of claims 1-9, wherein the method comprises co-administration of androgen in an amount equivalent to a daily oral dosage of 5 to 250 mg DHEA.

11. Use according to claim 9 or 10, wherein the estrogen and/or androgen is co-administered orally.

12. Use according to any one of claims 1-11, wherein the method comprises the co-administration of at least one anti-estrogen in an amount sufficient to impair the interaction of estrogens with estrogen receptors in the myomas, endometriotic, adenomyotic or endometrial tissue.

13. Use according to any one of claims 2-12, wherein the method comprises the co-administration of at least one anti-progestogen in an effective amount to boost the atrophic effect of the SEEM.

14. Use according to any of claims 1-13, wherein the benign gynaecological disorder is selected from the group consisting of uterine leiomyomas, adenomyosis and endometriosis.

15. Use according to any one of claims 1-14, wherein during treatment the blood serum estrogen level of the female is maintained at a level which is equivalent to at least 30 pg 17 β-estradiol /ml.

16. Use according to any one of claims 1-15, wherein the method comprises uninterrupted intravaginal administration of the SEEM for a period of at least 3 months, preferably at least 6 months

17. Drug delivery vehicle for intravaginal use, comprising at least 10 μg of a SEEM selected from the group consisting of aromatase inhibitors, 17β-hydroxysteroid dehydrogenase type 1 inhibitors and combinations thereof; and pharmaceutically acceptable excipient.

18. Drug delivery vehicle according to claim 17, wherein the drug delivery vehicle is a suppository, a tampon, a vaginal ring, tablet, capsule, cream, film, pessary, vaginal sponge, lotion, foam, ointment, paste, solution or a gel.

19. Drug delivery vehicle, according to claim 17 or 18, comprising at least 10 μg of anti-estrogen and/or 10 μg of anti-progestogen.

20. Pharmaceutical kit comprising a drug delivery vehicle according to claim 17 or 19 and a plurality of oral dosage units comprising estrogen in an amount equivalent to a dosage of at least 1 μg ethinyl estradiol and/or androgen in an amount equivalent to a dosage of 5 to 250 mg DHEA.

INTERNATIONAL SEARCH REPORT

Internati ...pplication No
PCT/NL 02/00513

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/00 A61K45/00 A61K45/06 A61P15/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 31631 A (RPMS TECHNOLOGY LTD) 4 September 1997 (1997-09-04) page 12, line 9 - line 15 page 12, line 30 -page 13, line 4 page 19, line 7 - line 9 page 20, line 19 -page 21, line 3 claims 5,7,11 ---	1-5,7,8, 15-18
X	DE 43 29 344 A (SCHERING AG) 2 March 1995 (1995-03-02) cited in the application page 2, line 3 - line 5 page 2, line 53 - line 62 page 3, line 49 - line 62 page 4, line 24 - line 58 examples 2,3,7 claims --- -/--	1-7,9-20

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 February 2003	14/02/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Epskamp, S

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INTERNATIONAL SEARCH REPORT

Internati pplication No
PCT/NL 02/00513

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DE 196 10 645 A (SCHERING AG) 11 September 1997 (1997-09-11) examples ---	17-20
X	US 6 274 573 B1 (KATSUKI YUKIO ET AL) 14 August 2001 (2001-08-14) cited in the application column 3, line 29 - line 41 column 6, line 31 -column 7, line 3 column 7, line 10 - line 39 claims ---	1-7,9-20
P,X	WO 02 20000 A (SLOAN KETTERING INST CANCER RES) 14 March 2002 (2002-03-14) page 13, line 21 - line 22; claims 13,15 ---	17-19
E	WO 02 072106 A (PHARMACIA ITALIA SPA) 19 September 2002 (2002-09-19) page 28, line 10 - line 20 ---	17,18
A	ZEITOUN KM ET AL: "Aromatase: a key molecule in the pathophysiology of endometriosis and a therapeutic target" FERTILITY AND STERILITY, vol. 72, no. 6, December 1999 (1999-12), pages 961-969, XP002211657 ISSN: 0015-0282 abstract page 963, left-hand column, paragraph 3 -page 964, left-hand column, paragraph 1; figures 2,3 page 964, right-hand column, paragraph 5 -page 965, right-hand column, paragraph 3; figure 5 page 966, right-hand column, paragraph 2 -page 977, right-hand column; figure 6 -----	1-20

Continuation of Box I.2

Present claims 1-20 relate to drugs defined by reference to their activity, namely "aromatase inhibitor", "cyclo-oxygenase 2 inhibitor", "17beta-hydroxysteroid dehydrogenase type 1 inhibitor", "estrogen", "androgen", "anti-estrogen", "anti-progestogen".
The subject-matter of the claims cover all drugs having (one of) these activities, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such drugs. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.
Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the drugs by reference to their activity. However, such a characterization can only be clear if instructions, in the form of experimental tests or any testable criteria, are available from the patent document or from general knowledge allowing the skilled person to recognize which active agents fall within the defined activity, and thus within the scope of the claims. Such instructions are however not provided. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.
Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the specific drugs (so with the exception of the "precursors" being referred to) which are listed in the description:
"aromatase inhibitor": see page 10, lines 28-30;
"cyclo-oxygenase 2 inhibitor": see page 11, lines 11-14;
"17beta-hydroxysteroid dehydrogenase type 1 inhibitor": see page 11, lines 16-23;
"estrogen": see page 15, lines 18-19;
"androgen": see page 18, lines 2-10;
"anti-estrogen": see page 16, lines 12 and 16-19;
"anti-progestogen": see page 19, line 19 - page 20, line 1.
Also the objected terms per se were included in the search.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Inter application No.
PCT/NL 02/00513

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: -
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Internati plication No
PCT/NL 02/00513

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