[0005] Although the pathogenesis has yet to be fully elucidated, the growth of uterine fibroids is known to be highly dependent on both estrogen and progestogen. Fibroids tend to shrink after menopause due to a decrease in hormone production.

[0006] Adenomyosis is a condition in which the inner lining of the uterus (the endometrium) breaks through the muscle wall of the uterus (the myometrium). Adenomyosis can cause menstrual cramps, lower abdominal pressure, and bloating before menstrual periods and can result in heavy periods. The condition can be located throughout the entire uterus or localized in one spot. Adenomyosis is a common condition. It is most often diagnosed in middle-aged women and women who have had children. Some studies also suggest that women who have had prior uterine surgery may be at risk for adenomyosis. Menorrhagia and intermenstrual bleeding are the most common complains, followed by pain, especially menstrual pain, and bladder and rectal pressure. Only surgery (myomectomy or hysterectomy) is regarded as curative.

[0007] Polycystic ovary syndrome (PCOS) is a hormonal disorder common among women of reproductive age. Women with PCOS may have infrequent or prolonged menstrual periods or excess male hormone (androgen) levels. The ovaries may develop numerous small collections of fluid (follicles) and fail to regularly release eggs.

[0008] Thus, there is a need in the art for new orally administered treatments for endometriosis, uterine fibroids, PCOS and adenomyosis and, in particular, management of pain associated with endometriosis, uterine fibroids, PCOS or adenomyosis and heavy menstrual bleeding associated with endometriosis, uterine fibroids, PCOS or adenomyosis. Moreover, there remains a need in the art to develop orally bioavailable dosage forms comprising such treatments and, in particular, a nonpeptide GnRH antagonist.

SUMMARY OF THE INVENTION

[0008a] In one aspect, provided herein is a solid pharmaceutical composition comprising 4-((R)-2-[5-(2-fluoro-3-methoxy-pheny1)-3-(2-fluoro-6-trifluoromethyl-benzy1)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-y1]-1-phenyl-ethylamino)-butyric acid (Compound A) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable meltable binder, wherein the weight ratio of Compound A or a pharmaceutically acceptable salt thereof to the pharmaceutically acceptable meltable binder is from about 1:1 to about 15:1.

[0008b] In another aspect, provided herein is a solid pharmaceutical composition as described herein, the composition comprising:

(a) from about 55% to about 60% by weight of amorphous sodium 4-((R)-2-[5-(2-fluoro-3-methoxy-pheny1)-3 -(2-fluoro-6-trifluoromethyl-benzy1)-4-methyl-2, 6-dioxo-3,6-dihydro-2H-pyrimidin-l-y1]-1-phenyl-ethylamino)butanoate;

(b) from about 4% to about 6% by weight of a pharmaceutically acceptable hydrophilic meltable polymer;

(c) from about 25% to about 35% by weight of a pH modifying agent;

(d) from about 4% to about 6% by weight of a disintegrant;

(e) from about 0.1% to about 2% by weight of a glidant; and

(f) from about 0.5% to about 1.5% by weight of a lubricant.

[0008c] In another aspect, provided herein is use of the solid pharmaceutical composition as described herein in the manufacture of a medicament for treating endometriosis, wherein the solid pharmaceutical composition as described herein is to be administered to a patient in need thereof.

[0008d] In another aspect, provided herein is use of the solid pharmaceutical composition as described herein in the manufacture of a medicament for treating uterine fibroids, wherein the solid pharmaceutical composition as described herein is to be administered to a patient in need thereof.

[0008e] In another aspect, provided herein is use of the solid pharmaceutical composition as described herein in the manufacture of a medicament for providing partial to substantially full suppression of estradiol in the treatment of a female patient with endometriosis or uterine fibroids, wherein the solid pharmaceutical composition as described herein is to be administered to the patient;

optionally wherein estradiol levels in the female patient are less than about 50 pg/mL;

optionally wherein estradiol levels in the female patient are less than about 20 pg/mL.

[0008f] In another aspect, provided herein is use of the solid pharmaceutical composition as described herein in the manufacture of a medicament for treating non-dominant adenomyosis or symptomatic adenomyosis, wherein the pharmaceutical composition as described herein is to be administered to a patient in need thereof;

optionally wherein Compound A is dosed 300 mg twice-a-day or 600 mg once-a-day.

[0008g] In another aspect, provided herein is use of a solid pharmaceutical composition in the manufacture of a medicament for treating heavy menstrual bleeding and pelvic pain in a woman with symptomatic adenomyosis, wherein a pharmaceutical composition comprising about 300 mg equivalent of Compound A is to be administered, wherein said composition includes:

(a) about 33.2% by weight of sodium 4-((R)-2-[5-(2-fluoro-3-methoxy-pheny1)-3-(2-fluoro-6-trifluoromethyl-benzy1)-4-methy1-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-y11-1 -phenyl-ethylamino)butanoate;

(b) about 16.7% by weight of an alkali metal salt; and

(c) about 51.1% by weight of one or more excipients, wherein the excipients comprises a binder, a water soluble filler, a lubricant, and a film-coating;

optionally said composition comprising:

(a) about 33.2% by weight of sodium 4-((R)-2-[5-(2-fluoro-3-methoxy-pheny1)-3-(2-fluoro-6-trifluoromethyl-benzy1)-4-methy1-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1 -y1]-1 -phenyl-ethylamino)butanoate;

(b) about 2.9% by weight of a binder;

(c) about 16.7% by weight of an alkali metal salt;

(d) about 41.6% by weight of a water soluble filler;

(e) about 1.8% by weight of a lubricant; and

(f) about 3.8% by weight of a film-coating; and/or

optionally wherein the treatment futher comprises an add-back therapy selected from a group consisting of estradiol, norethindrone acetate, or combinations thereof, optionally wherein the add-back therapy comprises 1 mg estradiol, 0.5 mg of norethindrone acetate, or combinations thereof and wherein the add-back therapy is to be administered once-a-day, to patients in need thereof.

[0008h] In yet another aspect, provided herein is use of a solid pharmaceutical composition in the manufacture of a medicament for treating heavy menstrual bleeding and pelvic pain in a woman with non-dominant adenomyosis, wherein a pharmaceutical composition comprising about 300 mg equivalent of Compound A is to be administered, wherein said composition includes:

a) about 33.2% by weight of sodium 4-((R)-2-[5-(2-fluoro-3-methoxy-pheny1)-3-(2-fluoro-6-trifluoromethyl-benzy1)-4-methy1-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-y1]-1-phenyl-ethylamino)butanoate;

b) about 16.7% by weight of an alkali metal salt; and

c) about 51.1% by weight of one or more excipients, wherein the excipients comprises a binder, a water soluble filler, a lubricant, and a film-coating;

optionally said composition comprising:

a) about 33.2% by weight of sodium 4-((R)-2-[5-(2-fluoro-3-methoxy-pheny1)-3-(2-fluoro-6-trifluoromethyl-benzy1)-4-methy1-2,6-dioxo-3,6-dihydro-21-1-pyrimidin-1-y1]-1 -phenyl-ethylamino)butanoate;

b) about 2.9% by weight of a binder;

c) about 16.7% by weight of an alkali metal salt;

d) about 41.6% by weight of a water soluble filler;

e) about 1.8% by weight of a lubricant; and

f) about 3.8% by weight of a film-coating; and/or

optionally wherein the treatment futher comprising an add-back therapy selected from a group consisting of estradiol, norethindrone acetate, or combinations thereof, optionally wherein the add-back therapy comprises 1 mg estradiol, 0.5 mg of norethindrone acetate, or combinations thereof and wherein the add-back therapy is to be administered once-a-day, to patients in need thereof.

[0008i] The solid pharmaceutical composition as described herein for use in therapy.

[0009] The disclosure is directed to solid pharmaceutical compositions comprising 4-((R)-2-[5-(2-fluoro-3-methoxy-phenyl)-3-(2-fluoro-6-trifluoromethyl-benzyl)-4-methyl-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-yl]-1-phenyl-ethylamino)-butyric acid (Compound A) or a pharmaceutically acceptable salt thereof; methods of using such compositions; and methods of achieving a high drug load of Compound A or a pharmaceutically acceptable salt thereof in such compositions.