VAGINAL INSERTED ESTRADIOL PHARMACEUTICAL COMPOSITIONS AND METHODS

CROSS-REFERENCES TO RELATED APPLICATIONS

The present application is a continuation of U.S. patent application Ser. No. 15/372,385, filed Dec. 7, 2016, which is a continuation-in-part of U.S. patent application Ser. No. 14/521,230, filed Oct. 22, 2014, and which claims priority to U.S. Provisional Pat. Appl. No. 62/264,309, filed Dec. 7, 2015; U.S. Provisional Pat. Appl. No. 62/296,552, filed Feb. 17, 2016; U.S. Provisional Pat. Appl. No. 62/324,838, filed Apr. 19, 2016; U.S. Provisional Pat. Appl. No. 62/329,940, filed Apr. 29, 2016; and U.S. Provisional Pat. Appl. No. 62/348,820, filed Jun. 10, 2016; which applications are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

This application is directed to pharmaceutical compositions, methods, and devices related to hormone replacement therapy.

BACKGROUND OF THE INVENTION

Postmenopausal women frequently suffer from atrophic vaginitis or vulvar and vaginal atrophy (hereinafter "vulvovaginal atrophy" or "VVA") with symptoms including, for example, vaginal dryness, vaginal odor, vaginal or vulvar irritation or itching, dysuria (pain, burning, or stinging when urinating), dyspareunia (vaginal pain associated with sexual activity), or vaginal bleeding associated with sexual activity. Other symptoms include soreness; with urinary frequency and urgency; urinary discomfort and incontinence also occurring ("estrogen-deficient urinary state(s)"). One symptom of vaginal atrophy is an increased vaginal pH, which creates an environment more susceptible to infections. The mucosal epithelium of the VVA patients also reported to show signs of severe atrophy and upon cytological examination accompanied by an increased number of the parabasal cells and a reduced number of superficial cells.

Each of these VVA-related states manifest symptoms associated with decreased estrogenization of the vulvovaginal tissue, and can even occur in women treated with oral administration of an estrogen-based pharmaceutical drug product. Although VVA is most common with menopausal women, it can occur at any time in a woman's life cycle. VVA symptoms also interfere with sexual activity and satisfaction. Women with female sexual dysfunction (FSD) are almost 4 times more likely to have VVA than those without FSD.

Estrogen treatment has proven to be very successful in controlling menopausal symptoms, including VVA and FSD. Several studies have shown that the symptoms connected with vaginal atrophy are often relieved by estrogen treatment given either systemically or topically. The existing treatments have numerous problems, for example compliance issues with patients not completing or continuing treatment due to the problems associated with the form of treatment.

Accordingly, there remains a need in the art for treatments for VVA and FSD that overcome these limitations.

BRIEF SUMMARY OF THE INVENTION

Disclosed herein is, among other things, a new soft gel vaginal pharmaceutical composition and dosage form containing solubilized estradiol for the treatment of VVA. The soft gel vaginal pharmaceutical composition has been designed to mitigate common limitations found with other vaginal forms of estradiol. The soft gel vaginal pharmaceutical composition eases vaginal administration, provides improved safety of insertion, minimizes vaginal discharge following administration, and provides a more effective dosage form having improved efficacy, safety and patient compliance.

According to various aspects and embodiments of this disclosure, a soft gel vaginal pharmaceutical composition as a treatment for post-menopausal women suffering with moderate to severe symptoms of VVA is provided.

Provided herein is a suppository comprising: a) a therapeutically effective amount of estradiol; and b) a solubilizing agent comprising a medium chain oil.

In some embodiments, the suppository includes about 1 μg to about 25 μg of estradiol. For example, the suppository can include about 1 μg to about 10 μg of estradiol; and about 10 μg to about 25 μg of estradiol.

In some embodiments, the estradiol is solubilized.

In some embodiments, the medium chain oil includes at least one C6-C12 fatty acid or a glycol, monoglyceride, diglyceride, or triglyceride ester thereof.

In some embodiments, the solubilizing agent includes at least one ester selected from the group consisting of: an ester of caproic fatty acid, an ester of caprylic fatty acid, an ester of capric fatty acid, and combinations thereof. For example, the solubilizing agent can include a caprylic/capric triglyceride.

In some embodiments, the suppository further includes a capsule. For example, the capsule can be a soft gelatin capsule.

Also provided herein is a suppository comprising: a) a therapeutically effective amount of estradiol; b) a caprylic/capric triglyceride; c) a non-ionic surfactant comprising PEG-6 stearate and ethylene glycol palmitostearate; and d) a soft gelatin capsule.

In some embodiments, a suppository provided herein includes about 25 μg of estradiol, wherein administration of the suppository to a patient provides, in a plasma sample from the patient: 1) a corrected geometric mean peak plasma concentration (C_{max}) of estradiol of about 19 pg/mL to about 29 pg/mL; and 2) a corrected geometric mean area under the curve $(AUC)_{0-24}$ of estradiol of about 75 pg*hr/mL to about 112 pg*hr/mL.

In some embodiments, a suppository provided herein includes about 25 μg of estradiol, wherein administration of the suppository to a patient provides, in a plasma sample from the patient: 1) a corrected geometric mean peak plasma concentration (C_{max}) of estrone of about 9 pg/mL to about 14 pg/mL; and 2) a corrected geometric mean area under the curve $(AUC)_{0-24}$ of estrone of about 43 pg*hr/mL to about 65 pg*hr/mL.

In some embodiments, a suppository provided herein includes about 25 μg of estradiol, wherein administration of the suppository to a patient provides, in a plasma sample from the patient: 1) a corrected geometric mean peak plasma concentration (C_{max}) of estrone sulfate of about 416 pg/mL to about 613 pg/mL; and 2) a corrected geometric mean area under the curve $(AUC)_{0-24}$ of estrone sulfate of about 3598 pg*hr/mL to about 5291 pg*hr/mL.

In some embodiments, a suppository provided herein includes about 10 μg of estradiol, wherein administration of the suppository to a patient provides, in a plasma sample from the patient: 1) a corrected geometric mean peak plasma concentration (C_{max}) of estradiol of about 12 pg/mL to about