PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr IMVEXXY ®

Estradiol vaginal inserts

Inserts, 4 mcg and 10 mcg estradiol, vaginal

House standard

Estrogen

Knight Therapeutics Inc.

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RECENT MAJOR LABEL CHANGES

7 WARNINGS AND PRECAUTIONS, Carcinogenesis and Mutagenesis	[10/2024]

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

IMVEXXY® (17 β-estradiol) is indicated for:

- the treatment of postmenopausal moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy.

IMVEXXY clinical effectiveness is supported by safety and efficacy data based on a 12-week study. The safety and efficacy of longer-term use of IMVEXXY have not been established (see 14 CLINICAL TRIALS).

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (>65 years of age): There have not been sufficient numbers of geriatric women involved in clinical studies utilizing IMVEXXY to determine whether those over 65 years of age differ from younger subjects in their response to IMVEXXY.

2 CONTRAINDICATIONS

IMVEXXY is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSTION AND PACKAGING.

IMVEXXY is contraindicated in women with any of the following conditions:

- Liver dysfunction or disease as long as liver function tests have failed to return to normal
- Known or suspected estrogen-dependent malignant neoplasia (e.g. endometrial cancer)
- Endometrial hyperplasia
- Known, suspected, or past history of breast cancer
- Undiagnosed abnormal genital bleeding
- Known or suspected pregnancy
- Active or past history of arterial thromboembolic disease (e.g. stroke, myocardial infarction, coronary heart disease)
- Active or past history of confirmed venous thromboembolism (such as deep vein thrombosis or pulmonary embolism) or active thrombophlebitis
- Partial or complete loss of vision due to ophthalmic vascular disease.

- Known protein C, protein S, or antithrombin deficiency, or other known thrombophilic disorders

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

The Women's Health Initiative (WHI) trial examined the health benefits and risks of oral combined *estrogen plus progestin* therapy (n=16,608) and oral *estrogen-alone* therapy (n=10,739) in postmenopausal women aged 50 to 79 years.

The *estrogen-alone* arm of the WHI trial (mean age 63.6 years) indicated an increased risk of *stroke* and *deep vein thrombosis* in hysterectomized women treated with CEE-alone (0.625 mg/day) for 6.8 years compared to those receiving placebo.

Therefore, the following should be given serious consideration at the time of prescribing:

- Estrogens with or without progestins **should not** be prescribed for primary or secondary prevention of cardiovascular diseases.
- Estrogens with or without progestins should be prescribed at **the lowest effective dose** for the approved indication.
- Estrogens with or without progestins should be prescribed for **the shortest period** possible for the approved indication.

IMVEXXY is a locally administered vaginal treatment containing 4 mcg or 10 mcg of estradiol and therefore the occurrence of the conditions mentioned in the box above, is less likely than with estrogen products used for systemic treatment. However, since IMVEXXY is a hormone therapy product these risks should be considered.

4 DOSAGE AND ADMINISTRATION

For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration should be used. Postmenopausal women should be re-evaluated periodically as clinically appropriate to determine if treatment is still necessary. (See 7 WARNINGS AND PRECAUTIONS)

IMVEXXY may be used in women with or without an intact uterus.
During treatment with IMVEXXY, even during the first 2 weeks, there was minimal systemic absorption and average plasma estradiol levels did not exceed postmenopausal levels.

IMVEXXY clinical effectiveness is supported by safety and efficacy data based on a 12 week study. The safety and efficacy of longer term use of IMVEXXY have not been established (see clinical trials).

4.1 Dosing Considerations

For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration should be used. Postmenopausal women should be re-evaluated periodically as clinically appropriate to determine if treatment is still necessary. (See 7 WARNINGS AND PRECAUTIONS)

IMVEXXY may be used in women with or without an intact uterus.
During treatment with IMVEXXY, even during the first 2 weeks, there was minimal systemic absorption and average plasma estradiol levels did not exceed postmenopausal levels.

IMVEXXY clinical effectiveness is supported by safety and efficacy data based on a 12-week study. The safety and efficacy of longer term use of IMVEXXY have not been established (see clinical trials).

4.2 Recommended Dose and Dosage Adjustment

Generally, women should be started at the 4 mcg dosage strength. Dosage adjustment should be guided by the clinical response.

Treatment may be started on any convenient day.

Initial dose:	1 vaginal insert daily at approximately the same time for 2 weeks
Maintenance dose:	1 vaginal insert twice weekly, every three to four days (for example, Monday and Thursday)

Pediatrics (<18 years of age): IMVEXXY is not indicated for use in the pediatric population.

4.4 Administration

IMVEXXY should be administered intravaginally by manual placement (without an applicator), by inserting the smaller end up for a depth of about two inches into the vaginal canal.

4.5 Missed Dose

If a patient misses a dose, it should be administered as soon as possible. If it is close to the patient's next scheduled dose, the missed dose should be skipped, and the patient should continue with her normal schedule. The patient should not insert two doses at the same time.

5 OVERDOSAGE

Numerous reports of ingestion of large doses of estrogen products and estrogen-containing oral contraceptives by young children have not revealed acute serious ill effects. Over dosage with estrogen may cause nausea, breast discomfort, fluid retention, bloating or vaginal bleeding in women.

Treatment of overdose consists of discontinuation of IMVEXXY therapy with institution of appropriate symptomatic care.

The dose of estradiol in IMVEXXY is very low compared with oral estrogen products.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Vaginal	Small, light pink, tear-shaped, softgel inserts of 4 mcg and 10 mcg estradiol.	Ethylene glycol palmitostearate, FD&C Red #40, gelatin, glycerin, hydrolyzed gelatin, lecithin, mannitol, medium chain triglycerides, pharmaceutical ink, polyethylene glycol stearates, purified water, sorbitan, sorbitol, titanium dioxide.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX at the beginning of Part I: Health Professional Information

General

IMVEXXY is a low-dose estrogen therapy product, intended only for vaginal administration. Systemic absorption may occur with the use of IMVEXXY (See 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics). IMVEXXY clinical effectiveness is supported by safety and efficacy data based on a 12-week study and current published evidence on the use of vaginal estrogen products. The following warnings and precautions associated with the use of systemic estrogen therapy should be taken into account in the absence of comparable data with other dosage forms of estrogens.

Carcinogenesis and Mutagenesis

Breast cancer

There is a need for caution in prescribing estrogens for women with known risk factors associated with the development of breast cancer, such as strong family history of breast cancer (first degree relative) or who present a breast condition with an increased risk (abnormal mammograms and/ or atypical hyperplasia at breast biopsy).

WHI Studies: In the *estrogen-alone* arm of the WHI trial, there was no statistically significant difference in the rate of invasive breast cancer in hysterectomized women treated with conjugated equine estrogens versus women treated with placebo. Extension of the WHI trials

also demonstrated an increased breast cancer risk associated with estrogen plus progestin therapy.

Epidemiological data/meta-analysis: Available epidemiological data indicate that the use of combined estrogen plus progestin by postmenopausal women is associated with an increased risk of invasive breast cancer. A large meta-analysis of prospective cohort studies based on 108, 647 postmenopausal women who developed breast cancer at mean age of 65 years old, also reported an increased risk of developing breast cancer in women treated with estrogen plus progestin therapy or estrogen alone therapy. Not only the risk of breast cancer increases with the duration of use, but also the risk could last up to >10 years after discontinuation of treatment. Observational studies also suggest that the risk of breast cancer was greater, and became apparent earlier, with estrogen plus progestin therapy as compared to estrogen-alone therapy. These studies have not generally found significant variation in the risk of breast cancer among different estrogen plus progestin combinations, doses, or routes of administration.

It is recommended that estrogens not be given to women with existing breast cancer or those with a previous history of the disease (see 2 CONTRAINDICATIONS).

Other known risk factors for the development of breast cancer such as nulliparity, obesity, early menarche, late age at first full term pregnancy and at menopause should also be evaluated.

It is recommended that women undergo mammography prior to the start of HRT treatment and at regular intervals during treatment, as deemed appropriate by the treating physician and according to the perceived risks for each patient.

The overall benefits and possible risks of hormone replacement therapy should be fully considered and discussed with patients.

Instructions for regular self-examination of the breasts should be included in this counseling.

Endometrial hyperplasia & endometrial carcinoma

An increased risk of endometrial hyperplasia/carcinoma has been reported with the use of unopposed estrogen therapy in a woman with a uterus. The reported endometrial cancer risk among unopposed estrogen users is about 2 to 12 times greater than in non-users and appears dependent on duration of treatment and on estrogen dose. Most studies show no significant increased risk associated with use of estrogens for less than 1 year. The greatest risk appears associated with prolonged use, with an increased risk of 15- to 24-fold for 5 to 10 years or more and this risk has been shown to persist for at least 8 to 15 years after estrogen therapy is discontinued.

There have been isolated post-market reports suggestive of possible systemic effects of estrogen associated with use of IMVEXXY (e.g. vaginal bleeding, exacerbation of, and new onset migraine headache, peripheral edema, and increased blood pressure). While no cases of endometrial cancer were reported in the pivotal trial, there was one case of proliferative

endometrium reported in IMVEXXY treated patients compared to no cases in the placebo-treated patients after only 12 weeks of treatment.

Clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including directed or random endometrial sampling when indicated, should be undertaken to rule out malignancy in postmenopausal women with undiagnosed persistent or recurring abnormal genital bleeding.

There is no evidence that the use of natural estrogens results in a different endometrial risk profile than synthetic estrogens of equivalent estrogen dose. Adding a progestin to estrogen therapy in postmenopausal women has been shown to reduce the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer.

Ovarian Cancer

Recent epidemiologic studies have found the use of hormone therapy (estrogen-alone and estrogen plus progestin therapies), in particular for five or more years, has been associated with an increased risk of ovarian cancer.

Cardiovascular

The results of the Heart and Estrogen/progestin Replacement Studies (HERS and HERS II) and the Women's Health Initiative (WHI) trial indicate that the use of *estrogen plus progestin* is associated with an increased risk of coronary heart disease (CHD) in postmenopausal women. The results of the WHI trial indicate that the use of *estrogen-alone* and *estrogen plus progestin* is associated with an increased risk of stroke in postmenopausal women.

WHI trial findings

In the *estrogen-alone* arm of the WHI trial of women with prior hysterectomy, among 10,000 women over a one-year period, there were/was:

- 12 more cases of stroke (44 on *estrogen-alone* therapy versus 32 on placebo)
- no statistically significant difference in the rate of CHD.

HERS and HERS II findings

In the Heart and Estrogen/progestin Replacement Study (HERS) of postmenopausal women with documented heart disease (n=2763, average age 66.7 years), a randomized placebo-controlled clinical trial of secondary prevention of coronary heart disease (CHD), treatment with 0.625 mg/day oral conjugated equine estrogen (CEE) plus 2.5 mg oral medroxyprogesterone acetate (MPA) demonstrated no cardiovascular benefit. Specifically, during an average follow-up of 4.1 years, treatment with CEE plus MPA did not reduce the overall rate of CHD events in postmenopausal women with established coronary heart disease. There were more CHD events in the hormone-treated group than in the placebo group in year 1, but not during the subsequent years.

From the original HERS trial, 2321 women consented to participate in an open label extension of HERS known as HERS II. Average follow-up in HERS II was an additional 2.7 years, for a total

of 6.8 years overall. After 6.8 years, hormone therapy did not reduce the risk of cardiovascular events in women with CHD.

Blood pressure

Women using hormone replacement therapy sometimes experience increased blood pressure. Blood pressure should be monitored with HRT use. Elevation of blood pressure in previously normotensive or hypertensive patients should be investigated and HRT may have to be discontinued.

Endocrine and Metabolism

Glucose and lipid metabolism

A worsening of glucose tolerance and lipid metabolism have been observed in a significant percentage of peri- and post-menopausal patients. Therefore, diabetic patients or those with a predisposition to diabetes should be observed closely to detect any alterations in carbohydrate or lipid metabolism, especially in triglyceride blood levels.

Women with familial hyperlipidemias or porphyria need special surveillance. Lipid lowering measures are recommended additionally, before treatment is started.

Calcium and phosphorus metabolism

Because the prolonged use of estrogens influences the metabolism of calcium and phosphorus, estrogens should be used with caution in patients with metabolic and malignant bone diseases associated with hypercalcemia and in patients with renal insufficiency.

Estrogens should be used with caution in individuals with severe hypocalcemia.

Estrogens should be used with caution in women with hypoparathyroidism as estrogen-induced hypocalcemia may occur.

Hypothyroidism

Patients who require thyroid hormone replacement therapy and who are also taking estrogen should have their thyroid function monitored regularly to assure that thyroid hormone levels remain in an acceptable range (see 9 DRUG INTERACTIONS, 9.7 Drug-Laboratory Test Interactions).

Genitourinary

Vaginal bleeding

Abnormal vaginal bleeding, due to its prolongation, irregularity or heaviness, occurring during therapy should prompt appropriate diagnostic measures to rule out the possibility of uterine malignancy and the treatment should be re-evaluated.

Uterine leiomyomata

Pre-existing uterine leiomyomata may increase in size during estrogen use. Growth, pain or tenderness of uterine leiomyomata requires discontinuation of medication and appropriate investigation.

Endometriosis

Symptoms and physical findings associated with a previous diagnosis of endometriosis may reappear or become aggravated with estrogen use.

Hematologic

Venous thromboembolism

Available epidemiological data indicate that use of estrogen with or without progestin by postmenopausal women is associated with an increased risk of developing venous thromboembolism (VTE).

In the *estrogen-alone* arm of the WHI trial, among 10,000 women on estrogen therapy over a one-year period, there were 7 more cases of venous thromboembolism, although there was no statistically significant difference in the rate of pulmonary embolism.

Generally recognized risk factors for VTE include a personal history, a family history (the occurrence of VTE in a direct relative at a relatively early age may indicate genetic predisposition), severe obesity (body mass index > 30 kg/m2) and systemic lupus erythematosus. The risk of VTE also increases with age and smoking.

The risk of VTE may be temporarily increased with prolonged immobilization, major surgery or trauma. In women on HRT, attention should be given to prophylactic measures to prevent VTE following surgery. Also, patients with varicose veins should be closely supervised. The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, retinal thrombosis, cerebral embolism and pulmonary embolism). If these occur or are suspected, hormone therapy should be discontinued immediately, given the risks of long-term disability or fatality.

If feasible, estrogens should be discontinued at least 4 weeks before major surgery which may be associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.

Hepatic/Biliary/Pancreatic

Gallbladder diseases

A 2- to 4-fold increase in the risk of gallbladder disease requiring surgery in women receiving postmenopausal estrogens has been reported.

Jaundice

Caution is advised in patients with a history of liver and/or biliary disorders. If cholestatic jaundice develops during treatment, the treatment should be discontinued, and appropriate investigations carried out.

Liver function tests

Liver function tests should be done periodically in subjects who are suspected of having hepatic disease. For information on endocrine and liver function tests, see the section under 7 WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests.

Monitoring and Laboratory Tests

Before IMVEXXY is administered, the patient should have a complete physical examination including a blood pressure determination. Breasts and pelvic organs should be appropriately examined and a Papanicolaou smear should be performed. Endometrial biopsy should be done only when indicated. Baseline tests should include mammography, measurements of blood glucose, calcium, triglycerides and cholesterol, and liver function tests.

The first follow-up examination should be done within 3-6 months after initiation of treatment to assess response to treatment. Thereafter, examinations should be made at intervals at least once a year. Appropriate investigations should be arranged at regular intervals as determined by the physician.

The importance of regular self-examination of the breasts should be discussed with the patient.

Laboratory test

Serum follicle stimulating hormone (FSH) and estradiol levels have not been shown to be useful in the management of moderate to severe symptoms of vulvar and vaginal atrophy due to menopause.

Neurologic

Cerebrovascular insufficiency

Patients who develop visual disturbances, classical migraine, transient aphasia, paralysis or loss of consciousness should discontinue medication.

Patients with a previous history of classical migraine and who develop a recurrence or worsening of migraine symptoms should be re-evaluated.

Dementia

Available epidemiological data indicate that the use of combined *estrogen plus progestin* in women age 65 and over may increase the risk of developing probable dementia.

The Women's Health Initiative Memory Study (WHIMS), a clinical substudy of the WHI, was designed to assess whether postmenopausal hormone replacement therapy (oral *estrogen plus progestin* or oral *estrogen-alone*) reduces the risk of dementia in women aged 65 and over (age range 65-79 years) and free of dementia at baseline.

In the *estrogen-alone* arm of the WHIMS (n=2947), women with prior hysterectomy were treated with daily 0.625 mg CEE or placebo for an average of 5.21 years. The results, when extrapolated to 10,000 women treated over a one-year period showed:

- 12 more cases of probable dementia (37 on *estrogen-alone* versus 25 on placebo), although this difference did not reach statistical significance.

Epilepsy

Particular caution is indicated in women with epilepsy, as HRT may cause an exacerbation of this condition.

Ophthalmologic

Retinal vascular thrombosis has been reported in women receiving estrogens. Discontinue medication pending examination if there is a sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, estrogens should be permanently discontinued.

Exacerbation of other conditions

Estrogen therapy may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine, porphyria, systemic lupus erythematosus, hepatic hemangiomas, of angioedema in women with hereditary angioedema. Estrogen should be used with caution in women with these conditions.

Renal

Fluid retention

Estrogens may cause fluid retention. Therefore, particular caution is indicated in cardiac or renal dysfunction, epilepsy or asthma. If, in any of the above-mentioned conditions, a worsening of the underlying disease is diagnosed or suspected during treatment, the benefits and risks of treatment should be reassessed based on the individual case.

7.1 Special Populations

7.1.1 Pregnant Women

Estrogen should not be used in pregnancy. Any possibility of pregnancy must be ruled out before prescribing IMVEXXY. If pregnancy occurs during IMVEXXY treatment, the medication should be discontinued immediately.

7.1.2 Breast-feeding

Estrogens should not be used during lactation. IMVEXXY should not be prescribed for nursing mothers.

7.1.3 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (>65 years of age): Clinical studies of IMVEXXY did not include a sufficient number of subjects aged 65 and over to determine if they responded differently from younger subjects.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

See 7 WARNINGS AND PRECAUTIONS regarding potential induction of malignant neoplasms and adverse effects similar to those of oral contraceptives.

The following adverse reactions have been reported with estrogen/progestin combination in general:

Blood and lymphatic system disorders

Altered coagulation tests (see 7 WARNINGS AND PRECAUTIONS, and 9 Drug Interactions, 9.7 Drug-Laboratory Test Interactions).

Cardiac disorders

Palpitations; increase in blood pressure (see 7 WARNINGS AND PRECAUTIONS); coronary thrombosis.

Endocrine disorders

Increased blood sugar levels; decreased glucose tolerance.

Eye disorders

Neuro-ocular lesions (e.g. retinal thrombosis, optic neuritis); visual disturbances; steepening of the corneal curvature; intolerance to contact lenses.

Gastrointestinal disorders

Nausea; vomiting; abdominal discomfort (cramps, pressure, pain, bloating).

General disorders and administration site conditions

Fatigue; changes in appetite; changes in body weight; change in libido.

Hepatobiliary disorders

Gallbladder disorder; asymptomatic impaired liver function; cholestatic jaundice.

Musculoskeletal and connective tissue disorders

Musculoskeletal pain including leg pain not related to thromboembolic disease (usually transient, lasting 3-6 weeks) may occur.

Nervous system disorders

Aggravation of migraine episodes; headaches; dizziness; neuritis.

Psychiatric disorders

Mental depression; nervousness; irritability.

Renal and urinary disorders

Cystitis; dysuria; sodium retention; edema.

Reproductive system and breast disorders

Breakthrough bleeding; spotting; change in menstrual flow; dysmenorrhea; vaginal itching/discharge; dyspareunia; endometrial hyperplasia; pre-menstrual-like syndrome; reactivation of endometriosis; changes in cervical erosion and amount of cervical secretion; breast swelling and tenderness.

Skin and subcutaneous tissue disorders

Chloasma or melasma, which may persist when drug is discontinued; erythema multiforme; erythema nodosum; haemorrhagic eruption; loss of scalp hair; hirsutism and acne.

Vascular disorders

Isolated cases of: thrombophlebitis; thromboembolic disorders.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Table 2 - Treatment-Related Treatment Emergent Adverse Events Reported at a Frequency of ≥ 1% in IMVEXXY 4 mcg and 10 mcg Groups and at an Incidence Greater than in the Placebo Group (Safety Population)

System Organ Class MedDRA Preferred Term	IMVEXXY 4 mcg (N=191) n (%)	IMVEXXY 10 mcg (N=215) n (%)	Placebo (N=218) n (%)
Gastrointestinal disorders			
Abdominal pain	2 (1.0)	2 (0.9)	1 (0.5)
Nausea	2 (1.0)	1 (0.5)	0 (0.0)
Diarrhoea	2 (1.0)	0 (0.0)	0 (0.0)
General disorders and administration site conditions			
Irritability	2 (1.0)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorders			
Muscle spasms	2 (1.0)	2 (0.9)	0 (0.0)
Nervous system disorders			
Headache	7 (3.7)	5 (2.3)	6 (2.8)
Reproductive system and breast disorders			
Vaginal discharge	5 (2.6)	7 (3.3)	12 (5.5)
Pelvic pain	3 (1.6)	2 (0.9)	2 (0.9)
Vaginal haemorrhage	2 (1.0)	2 (0.9)	3 (1.4)

System Organ Class MedDRA Preferred Term	IMVEXXY 4 mcg (N=191) n (%)	IMVEXXY 10 mcg (N=215) n (%)	Placebo (N=218) n (%)
Vulvovaginal discomfort	3 (1.6)	0 (0.0)	1 (0.5)
Vaginal odor	3 (1.6)	0 (0.0)	1 (0.5)

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

No data available. IMVEXXY is not indicated for pediatric patients.

8.3 Less Common Clinical Trial Adverse Reactions

Cardiac disorders: palpitations.

Gastrointestinal disorders: abdominal distension, abdominal pain lower, abdominal pain upper, dyspepsia**,** gastroesophageal reflux disease.

General disorders and administration site conditions: fatigue, hyperhidrosis, oedema peripheral.

Infections and infestations: vulvovaginal candidiasis, vulvovaginal mycotic infection.

Injury, poisoning and procedural complications: vulvar laceration.

Investigations: blood alkaline phosphate increased, blood bilirubin increased, blood glucose increased, blood iron decreased, blood pressure increased, electrocardiogram change.

Metabolism and nutrition disorders: hypercholesterolaemia.

Nervous system disorders: cluster headache, dizziness, migraine.

Psychiatric disorders: anxiety.

Renal and urinary disorders: dysuria, haematuria.

Reproductive system and breast disorders: breast tenderness, cervical dysplasia, hot flush, perineal ulceration, vaginal dysplasia, vulvovaginal burning sensation, vulvovaginal erythema, vulvovaginal pain, vulvovaginal pruritus.

Respiratory, thoracic and mediastinal disorders: cough.

Skin and subcutaneous tissue disorders: acne, blister, bromhidrosis, chloasma, pruritus, rash.

Vascular disorders: hypertension.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

There were no clinically meaningful changes in the mean hematology values, mean blood chemistry values, or any urinalysis parameters, between Baseline and Week 12 (Follow-up) in women treated with IMVEXXY 4 or 10 mcg, or with placebo.

8.5 Post-Market Adverse Reactions

No data available.

If adverse symptoms persist, the prescription of HRT should be re-considered.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Estrogens may diminish the effectiveness of anticoagulant, antidiabetic and antihypertensive agents.

Preparations inducing liver enzymes (e.g. barbiturates, hydantoins, carbamazepine, meprobamates, phenylbutazone or rifampicin) may interfere with the activity of orally administered estrogens.

9.3 Drug-Behavioural Interactions

No data available.

9.4 Drug-Drug Interactions

No drug-drug interaction studies have been conducted with IMVEXXY.

As the estrogen in IMVEXXY is administered within the vagina and due to the low levels of estradiol absorption, it is unlikely that any clinically relevant drug interactions will occur with IMVEXXY.

However, the metabolism of estrogens may be increased by concomitant use of substances known to induce drug-metabolizing enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants (e.g. phenobarbital, phenytoin, carbamazepine) and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz).

Ritonavir and nelfinavir, although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones.

9.5 Drug-Food Interactions

No drug-food interaction studies have been conducted with IMVEXXY.

9.6 Drug-Herb Interactions

No drug-herb interaction studies have been conducted with IMVEXXY.

It was found that some herbal products (e.g. St. John's wort) which are available as over-the-counter (OTC) products might interfere with steroid metabolism and therefore alter the efficacy and safety of estrogen/progestin products.

Physicians and other health care providers should be made aware of other non-prescription products concomitantly used by the patient, including herbal and natural products obtained from the widely spread health stores.

9.7 Drug-Laboratory Test Interactions

The results of certain endocrine and liver function tests may be affected by estrogen-containing products:

- increased prothrombin time and partial thromboplastin time; increased levels of fibrinogen and fibrinogen activity; increased coagulation factors VII, VIII, IX, X; increased norepinephrine-induced platelet aggregability; decreased antithrombin III;
- increased thyroxine-binding globulin (TBG), leading to increased circulating total thyroid hormone (T4) as measured by column or radioimmunoassay; T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered;
- other binding proteins may be elevated in serum i.e., corticosteroid binding globulin (CBG), sex-hormone binding globulin (SHBG), leading to increased circulating corticosteroids and sex steroids respectively; free or biologically active hormone concentrations are unchanged;
- impaired glucose tolerance;
- increased serum triglycerides and phospholipids concentration;

The results of the above laboratory tests should not be considered reliable unless therapy has been discontinued for two to four weeks.

The pathologist should be informed that the patient is receiving hormone replacement therapy (HRT) when relevant specimens are submitted.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

IMVEXXY is a softgel vaginal formulation containing estradiol, an estrogen. IMVEXXY vaginal insert are used intravaginally. When the insert comes in contact with the vaginal mucosa, estradiol is released into the vagina. Low-dose vaginal estrogen products result in low systemic estrogen exposure.

10.2 Pharmacodynamics

Currently, there are no pharmacodynamics data known for IMVEXXY.

10.3 Pharmacokinetics

Absorption:

Estrogen drug products are well absorbed through the skin, mucous membranes, and the gastrointestinal tract. The vaginal delivery of estrogens circumvents first-pass metabolism.

In a multicenter, double-blind placebo-controlled study of 574 postmenopausal women randomized to placebo, or 4 and 10 mcg of IMVEXXY, a subset of 54 women participated in a pharmacokinetics substudy. Women received 1 vaginal insert daily for the first 2 weeks, followed by 1 insert twice weekly for the following 10 weeks.

Mean (±SD) serum estradiol and estrone following 14 days of once daily administration of IMVEXXY are shown in Figure 1. Administration of the 4 mcg and 10 mcg IMVEXXY vaginal inserts and placebo once daily for 14 days resulted in a mean estradiol $C_{avg\ (0\text{-}24)}$ of 3.6, 4.6, and 4.3 pg/mL, respectively, Table 3.

Figure 1: Mean (±SD) Serum Concentration of Estradiol and Estrone on Day 14 Following Daily Administration of IMVEXXY 4 mcg, IMVEXXY 10 mcg, and Placebo

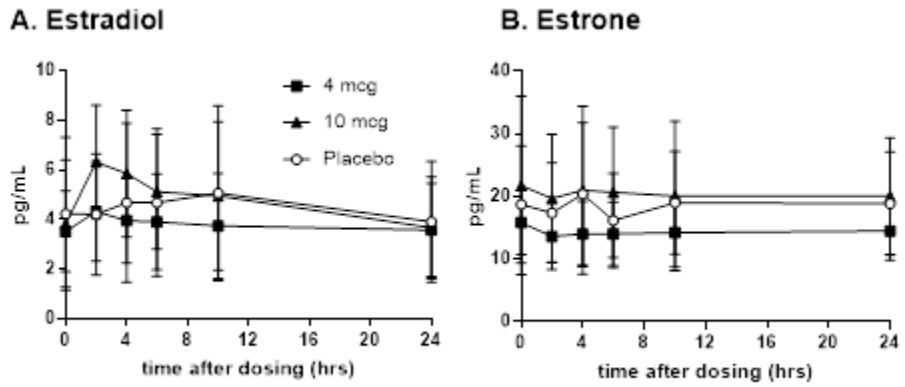


Table 3 - Arithmetic Mean (SD) of Estradiol and Estrone Pharmacokinetic Parameters Following 14 Daily Doses – Unadjusted for Baseline

	Estradiol		Estrone	
	C_{max} (pg/mL)	$C_{avg\ (0\text{-}24)}$ (pg/mL)	C_{max} (pg/mL)	$C_{avg\ (0\text{-}24)}$ (pg/mL)
IMVEXXY 4 mcg	4.8 (2.3)	3.6 (1.8)	16.0 (5.5)	13.6 (4.8)
IMVEXXY 10 mcg	7.3 (2.4)	4.6 (2.3)	23.9 (13.4)	19.3 (10.2)
Placebo	5.5 (3.4)	4.3 (2.8)	22.8 (10.9)	17.8 (7.5)

At Day 84, estradiol concentrations compared to Baseline concentrations were: 4.3 vs 3.9 pg/mL for IMVEXXY 4 mcg; 4.8 vs 5.0 pg/mL for IMVEXXY 10 mcg; and 4.4 vs 4.5 pg/mL for placebo.

Distribution:

The distribution of exogenous estrogens is similar to that of endogenous estrogens. Estrogens are widely distributed in the body and are generally found in higher concentrations in the sex

hormone target organs. Estrogens circulate in the blood largely bound to SHBG and albumin.

Metabolism:

Exogenous estrogens are metabolized in the same manner as endogenous estrogens. Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. These transformations take place mainly in the liver. Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is the major urinary metabolite. Estrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the intestine followed by reabsorption. In postmenopausal women, a significant portion of the circulating estrogens exist as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active estrogens.

Elimination:

Estradiol, estrone, and estriol are excreted in the urine along with glucuronide and sulfate conjugates.

Special Populations and Conditions

No pharmacokinetic studies were conducted in specific populations, including women with renal or hepatic impairment.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15-25°C).

Keep in a safe place out of the reach and sight of children.

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

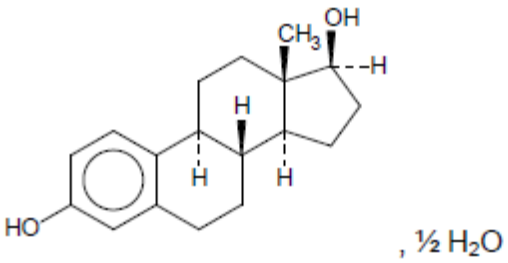
Proper name: estradiol

Chemical name: estra-1,3,5 (10)-triene-3,17β-diol hemihydrate

Molecular formula: $C_{18}H_{24}O_2 \bullet ½\ H2O$

Molecular mass: 281.4 g/mol

Structural formula:



Physicochemical properties: white or almost white, crystalline powder, or colorless crystals. Practically insoluble in water, soluble in acetone and ethanol (96%); slightly soluble in ether and methylene chloride. It has a specific optical rotation of +76° to +83° and a melting range of 173°C to 179°C.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Postmenopausal Moderate to Severe Dyspareunia

Table 4 - Summary of patient demographics for clinical trials in postmenopausal women with moderate to severe symptoms of vulvar and vaginal atrophy

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)	Sex
TV14-01	Randomized, double-blind, placebo-controlled, parallel-group trial	4 mcg, 10 mcg, placebo vaginal inserts 12 weeks	191 191 192	59.1 (40-75)	Postmenopausal women

The effectiveness and safety of two doses IMVEXXY (4 µg, and 10 µg) compared with placebo at 12 weeks on vaginal superficial cells, vaginal parabasal cells, vaginal pH, and the symptom of moderate to severe dyspareunia (vaginal pain associated with sexual activity) as the most bothersome symptom (MBS) associated with VVA, were examined in one placebo-controlled clinical trial.

This 12-week, randomized, double-blind, placebo-controlled, parallel-group trial enrolled 574 generally healthy postmenopausal women between 40 to 75 years of age (mean 59 years of age) who at baseline assessment had ≤5 percent superficial cells on a vaginal smear, a vaginal pH >5.0, and also identified, at baseline, moderate to severe dyspareunia as the most bothersome symptom to her. Greater than 90% of women also reported moderate to severe vaginal dryness at baseline.

All women were assessed for improvement in the mean change from Baseline to Week 12 for the co-primary efficacy variables of: most bothersome moderate to severe symptom of dyspareunia, percentage of vaginal superficial and percentage of vaginal parabasal cells on a vaginal smear, and vaginal pH.

Study Results

PRIMARY ENDPOINTS

IMVEXXY 4 mcg and 10 mcg inserts were statistically superior to placebo in reducing the severity of moderate to severe dyspareunia at Week 12. (See Table 5). A statistically significant increase in the percentage of superficial cells and a corresponding statistically significant decrease in the percentage of parabasal cells on a vaginal smear was also demonstrated for

IMVEXXY 4 mcg and 10 mcg inserts (p<0.0001). The mean reduction in vaginal pH between Baseline and Week 12 was also statistically significant for IMVEXXY 4 mcg and 10 mcg inserts (p<0.0001).

Table 5 - Efficacy Summary Associated with Postmenopausal Vulvar and Vaginal Atrophy (Least Square Mean Change from Baseline to Week 12)

Parameter	IMVEXXY 4 µg (N=186)	IMVEXXY 10 µg (N=188)	Placebo (N=187)
Percent Change in Parabasal Cells (n)	170	171	172
LS Mean (SE)	-40.63 (1.755)	-44.07 (1.751)	-6.73 (1.750)
MMRM P-value vs placebo	<0.0001	<0.0001	---
Percent Change in Superficial Cells (n)	170	171	172
LS Mean (SE)	17.50 (1.542)	16.72 (1.540)	5.63 (1.537)
MMRM P-value vs placebo	<0.0001	<0.0001	---
Change in Vaginal pH (n)	170	171	174
LS Mean (SE)	-1.32 (0.066)	-1.42 (0.066)	-0.28 (0.066)
MMRM P-value vs placebo	<0.0001	<0.0001	---
Change in Severity of Dyspareunia (n)	151	154	163
LS Mean (SE)	-1.52 (0.071)	-1.69 (0.071)	-1.28 (0.070)
MMRM P-value vs placebo	0.0149	<0.0001	---

The modified intent-to-treat population (MITT) included only women in the ITT population who at baseline met the inclusion criteria of ≤5 percent superficial cells on a vaginal smear, a vaginal pH >5.0, and who identified moderate or severe dyspareunia as her most bothersome vaginal symptom.
Abbreviations: LS - least square; MITT - modified intent-to-treat; SE - standard error; MMRM - Mixed Model Repeated Measures

The percentage of subjects reporting no dyspareunia at the end of the study was 25.8%, and 32.4%, vs 19.8% in IMVEXXY 4 µg, and 10 µg, and placebo, respectively.

SECONDARY ENDPOINTS

The change from Baseline to Weeks 2, 6, and 8 in percentage of **parabasal** and **superficial cells** was statistically different at each time point and for both doses of IMVEXXY compared to placebo (p<0.0001).

The change from Baseline to Weeks 2, 6, and 8 in **vaginal pH** was statistically decreased at each time point (by more than one unit) and for the two doses of IMVEXXY compared to placebo (p<0.0001).

The change from Baseline to Weeks 2, 6, and 8 in the **severity of dyspareunia** was statistically significantly reduced at each time point and for the two doses of IMVEXXY compared to

placebo.

The percentage of subjects reporting no **vaginal dryness** at the end of the study was 31.2%, and 36.7%, vs 17.1% in IMVEXXY 4 µg, and 10 µg, and placebo, respectively. Additionally, the severity of dryness at the end of the study improved by 2 to 3 levels in 38.2% of subjects in the IMVEXXY 4 µg group, 47.4% in the IMVEXXY 10 µg group compared to 28.9% in the placebo group.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

Long-term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis, and liver.

Carcinogenicity

Carcinogenicity studies with IMVEXXY have not been conducted. Carcinogenicity of 17β-estradiol is well-established in the literature.

Long-term studies in mice demonstrate that oral administration of 0.00188, 0.015, 0.15 and 0.75 mg/kg/day in mice can increased the incidences of mammary, uterine, cervical and ovarian tubular tumours. In rats administered 10-12 mg/animal by subcutaneous pellet, there was an increased incidence of mammary and pituitary tumours.

Genotoxicity

Genotoxicity studies with IMVEXXY have not been conducted. Genotoxicity of 17β-estradiol is well-established in the literature.

The clastogenic potential of 17 β-estradiol was evident from the chromosome aberrations and sister chromatid exchanges induced with and without metabolic activation in cultured human lymphocytes and from the increased frequencies of micronuclei formation and sister chromatid exchanges in mice. However, 17 β-estradiol is not considered to be mutagenic as a negative response was observed in the in vitro Ames bacterial reverse mutation assay.

Reproductive and Developmental Toxicology

Animal fertility studies have not been performed with IMVEXXY. Reproductive toxicity of 17β-estradiol is well-established in the literature.

17 β-estradiol administered in the feed to female Crl:CD BR rats at doses equal to 0, 0.003, 0.173, 0.691, or 4.12 mg/kg/day and to males at doses equal to 0, 0.003, 0.139, 0.527, or 3.16 mg/kg/day resulted in a decreased in the number of matings and no pregnancies at the two

highest doses. For the three groups with pregnancies (0, 0.003, 0.173 mg/kg/day), there was no difference in gestation length, however, gestation body weight gain, food consumption, and mean number of implants were affected. Mean number of live births was significantly decreased in the 0.173 mg/kg/day group compared to control.

Parental administration of 17 β-estradiol did not affect the anogenital distance in male or female pups. Onset of sexual maturity, as measured by prepubertal separation in males, was significantly delayed in the 0.17 mg/kg/day group. Onset of sexual maturity, as measured by vaginal opening in females, was decreased in both the 0.003 and 0.173 mg/kg/day dosed groups (24/56 female pup were vaginally patent on the day of weaning. The F1 generation was not mated.

In white rabbits, intramuscular estradiol administration at 15 or 30 µg/animal for 3-6 consecutive days at different times during gestation resulted in 67 and 78% aborted or totally resorbed litters and 4% and 17% of litters with dead fetuses, respectively.

Special Toxicology

Local Tolerance
A local tolerability study was conducted in rabbits to assess the potential for Miglyol® 812, an excipient having a suitable ability to dissolve 17 β-estradiol, to cause vaginal irritation.

Rabbits were administered 17 β-estradiol insert containing Miglyol 812 for 28 days via vaginal gavage at total daily doses of 0.3, 0.6, and 1.2 mL/animal/day, which corresponds to total daily Miglyol 812 doses of 0, 270, 540, and 1080 mg/day (0, ~103, ~189, and ~376 mg/kg based on mean terminal body weights).

Study demonstrated that the pharmaceutical excipient Miglyol® 812 was non-irritating to the vagina following repeated daily administration for 28 days.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]IMVEXXY®

estradiol vaginal inserts

Read this carefully before you start taking **IMVEXXY** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **IMVEXXY**.

Serious Warnings and Precautions

The Women's Health Initiative (WHI) trial was a large clinical study. This study assessed the benefits and risks of two oral therapies (combined estrogen plus progestin and estrogen-alone) compared with placebo (a pill with no active ingredients) in postmenopausal women.

In postmenopausal women taking oral estrogen-alone, who had a prior surgery to remove the uterus (called a hysterectomy), the WHI trial indicated an increased risk of stroke and deep vein thrombosis.

Therefore, you should highly consider the following:

- There is an increased risk of stroke and blood clots in the large veins with the use of oral estrogen-alone therapy.
- Estrogens with or without progestins should not be used for the prevention of heart disease or stroke.
- Estrogens with or without progestin should be used at the lowest effective dose and for the shortest period of time possible. Regular medical follow-up is advised.

What is IMVEXXY used for?

- IMVEXXY is used to treat postmenopausal women who experience pain before, during or after sex. This is a symptom of vulvar and vaginal atrophy (thinning, drying and inflammation of the vulva and vagina).

The safe and effective use of IMVEXXY for more than 12 weeks has not been studied.

You should carefully discuss the risks and benefits of hormone replacement therapy (HRT) with your healthcare professional. You should regularly talk with your healthcare professional about whether you still need treatment with HRT.

How does IMVEXXY work?

After menopause, your body stops making the female hormone estrogen. IMVEXXY contains estradiol, which is a type of estrogen. It replaces the estrogen that some women are missing in

the vagina. This may help reduce dryness and discomfort around your vagina, which can improve pain before, during or after sex.

What are the ingredients in IMVEXXY?

Medicinal ingredients: estradiol as estradiol hemihydrate.

Non-medicinal ingredients: ethylene glycol palmitostearate, FD&C Red #40, gelatin, glycerin, hydrolyzed gelatin, lecithin, mannitol, medium chain triglycerides, pharmaceutical ink, polyethylene glycol stearates, purified water, sorbitan, sorbitol, titanium dioxide.

IMVEXXY comes in the following dosage forms:

Softgel vaginal inserts of 4 mcg and 10 mcg.

Do not use IMVEXXY if:

- you are allergic to estradiol or to any of the non-medicinal ingredients in IMVEXXY or a component of the container (see **What are the ingredients in IMVEXXY?**)
- you are pregnant or think you may be pregnant
- you have or have had liver problems, and blood tests to measure how your liver is working have not returned to normal
- you have, might have or had cancer that is sensitive to estrogen (e.g. breast cancer or endometrial cancer)
- your uterus lining is thicker than normal (endometrial hyperplasia)
- you have or have had breast cancer, or you are suspected of having it
- you have unexplained bleeding from the vagina
- you have recently had a heart attack, stroke, a blockage or narrowing of the arteries around the heart (called coronary heart disease)
- you have or have had blood clotting problems:
    - deep vein thrombosis (blood clots in big veins)
    - pulmonary embolism (blood clots in the lung)
    - thrombophlebitis (inflammation of a vein caused by a blood clot)
    - protein C, protein S, or anti-thrombin deficiency
- you have eye problems that are caused by low blood flow to the eye

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take IMVEXXY. Talk about any health conditions or problems you may have, including if you:

- have or had uterus problems:
    - fibroids (growths) inside your uterus
    - endometriosis (growth of the uterine lining outside your uterus)
    - a history of endometrial hyperplasia (overgrowth of the lining of the uterus)
    - have had a hysterectomy (surgical removal of the uterus).

- have a history of allergy or intolerance to any drugs or other substances
- have a history of liver problems, yellowing of the eyes and/or skin (jaundice) or itching
- have symptoms of blood blockage to the brain
    - migraine, headaches, trouble speaking, paralysis, loss of consciousness.
- have or had high blood pressure;
- have or had asthma
- have kidney problems
- have seizures (epilepsy)
- have or had bone disease (this includes certain conditions or cancers that can affect blood levels of calcium and phosphorus)
- have or had diabetes or a family history of diabetes
- have or had high levels of fat in your blood (cholesterol, triglycerides)
- are breastfeeding
- smoke
- have or had an autoimmune disease
- had or will have surgery
- have a disease that affects how the blood functions (porphyria)
- have low or high levels of calcium
- Have thyroid problems
- Have biliary problems (gallbladder disease, bile problems);
- Have eye problems

Other warnings you should know about:

Cancer:

- **Breast cancer:** The results of the WHI trial indicated an increased risk of breast cancer in post-menopausal women taking combined estrogen plus progestin compared to women taking placebo.

  The results of the WHI trial indicated no difference in the risk of breast cancer in postmenopausal women with prior hysterectomy taking estrogen-alone compared to women taking placebo.

  There is an increased risk for breast cancer in women taking menopausal HRT for many years. The risk increases the longer you take HRT and persists for more than 10 years after stopping treatment with both estrogen plus progestin therapy and estrogen-alone therapy.

  If you have had breast cancer, you should not take estrogens with or without progestins.

  If you have a family history of breast cancer or have had breast lumps, breast biopsies or abnormal mammograms (breast x-rays), talk to your healthcare professional before starting HRT.

  Women should have a mammogram before starting HRT and at regular intervals during treatment as recommended by their healthcare professional.

Regular breast examinations by a healthcare professional and regular self-breast examinations are recommended for all women. You should review techniques for breast self-examination with your healthcare professional.

The increased risk of breast cancer in patients taking estrogen-alone is lower than in patients using combined (estrogen-progestogen) HRT.

- **Ovarian cancer:** Women who take estrogen-only or combined HRT for 5 or more years have a slightly higher chance of ovarian cancer.

Overgrowth of the lining of the uterus and cancer of the uterus:

There was one report of proliferative endometrium (uterus lining growth) seen in women using IMVEXXY.

The use of estrogen-alone therapy increases the risk of developing endometrial hyperplasia (overgrowth of the lining of the uterus). The risk of endometrial cancer (cancer of the lining of the uterus) increases the longer you use estrogen-alone therapy. These risks apply to post-menopausal women with a uterus.

Talk to your healthcare professional about the risk factors for overgrowth and cancer of the uterus lining. They should discuss ways to reduce the risks, including progestin treatments.

You should also report any unexpected or unusual vaginal bleeding.

Heart disease (heart attack) and stroke:

The WHI trial showed:

- An increased risk of stroke and coronary heart disease in postmenopausal women taking combined estrogen plus progestin.
- An increased risk of stroke, but no difference in the risk of coronary heart disease in postmenopausal women with a previous hysterectomy taking estrogen-alone.

Abnormal blood clotting (including pulmonary embolism and deep vein thrombosis): The WHI trial showed:

- An increased risk of pulmonary emboli and deep vein thrombosis (blood clots in the lung and in big veins) in postmenopausal women taking combined estrogen plus progestin.
- An increased risk of deep vein thrombosis, but no difference in the risk of pulmonary emboli in postmenopausal women with previous hysterectomy taking estrogen-alone.

You are more likely to get a blood clot in your veins as you get older. Blood clots can be life-threatening or cause serious disability. Talk to your healthcare professional if any of the below situations apply to you:

- you use estrogens
- you are overweight and your BMI is greater than 30
- you have any blood clotting problem that needs long-term treatment with a medicine used

to prevent blood clots
- any of your close relatives has ever had a blood clot in the leg, lung or another organ
- you smoke
- you have systemic lupus erythematosus (an autoimmune disease)
- you have cancer

The risk for blood clots is also temporarily higher if you are immobilized for long periods of time and following major surgery. If you are going to have a surgery, tell your healthcare professional that you are taking IMVEXXY. You may need to stop taking IMVEXXY at least 4 weeks before the surgery to reduce the risk of a blood clot. Ask your healthcare professional when you can start taking IMVEXXY again.

Gallbladder disease: The use of estrogens by postmenopausal women has been associated with an increased risk of gallbladder disease that needs surgery.

Dementia: The Women's Health Initiative Memory Study (WHIMS) was a sub-study of the WHI trial. The WHIMS study showed:

- An increased risk of dementia (loss of memory and intellectual function) in postmenopausal women age 65 and over who were taking oral combined estrogen plus progestin.
- No difference in the risk of dementia in postmenopausal women aged 65 and over who had previously had a hysterectomy and were taking oral estrogen-alone.

Physical exam, tests, and check-ups: Before you start taking IMVEXXY, you will need to have examinations and tests. These will include a physical exam, a Pap smear and a breast exam. Your healthcare professional will ask you about your personal and your family's health history. You will also have your blood pressure taken as well as blood tests and a mammogram (breast x-ray). A uterus tissue sample might be needed.

While you are taking IMVEXXY, check your breasts often and get regular check-ups with your healthcare professional.

Your first check-up should be within 3 to 6 months of starting IMVEXXY. Thereafter, these should be scheduled at least once a year. These check-ups will help to identify any side effects you may have. Your visits may include a blood pressure check, a breast exam, a Pap smear, and pelvic exam. You will also have repeat mammograms and blood tests. Your healthcare professional will decide when these are necessary and will interpret the results.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with IMVEXXY:

- medicines used to treat diabetes, such as glyburide and insulin.
- medicines used for the prevention or treatment of blood clots (anticoagulants), such as warfarin

- medicines used to treat high blood pressure, such as verapamil and diltiazem
- Medicines used to help you relax or sleep, such as barbiturates and meprobamates
- phenylbutazone, a nonsteroidal anti-inflammatory drug (NSAID) used to treat fever, pain and inflammation
- rifampicin, used to treat tuberculosis
- phenobarbital, phenytoin, hydantoins, carbamazepine, used to treat epilepsy and seizures
- ritonavir and nelfinavir, used to treat HIV/AIDS
- St. John's Wort, used to treat depression

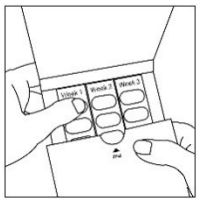
How to use IMVEXXY:

- Use IMVEXXY exactly as directed by your healthcare professional.
- Do not use more than the recommended dose prescribed by your healthcare professional.
- Do not change the dose or schedule unless your healthcare professional tells you to.
- IMVEXXY is a vaginal insert that you place in your vagina.
- IMVEXXY is only for use in the vagina (without an applicator).
- **Do not take IMVEXXY by mouth (orally).**

Step 1:

- Push one IMVEXXY insert through the foil of the blister package (Figure A).

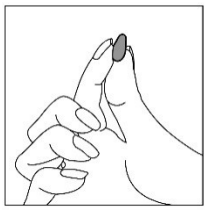
Figure A



Step 2:

- Hold the IMVEXXY insert with the larger end between your fingers (Figure B).

Figure B

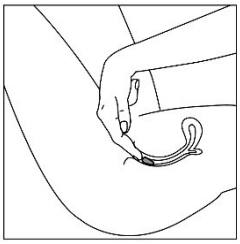


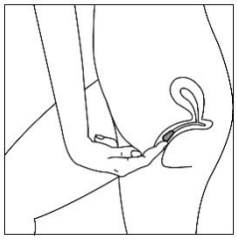
Step 3:

- To place the vaginal insert, select the position that is most comfortable for you. See Figure C for the lying down position or Figure D for the standing position.

- With the smaller end up, put the insert about two inches into your vagina using your finger.

Figure C **or** **Figure D**





Usual dose:

Starter Dosage (First Two Weeks):

1. Wash and dry your hands before handling the IMVEXXY insert.
2. Place one vaginal insert into your vagina, once per day at about the same time, for the first two weeks.
3. Write down the days you will put in your IMVEXXY insert.

Maintenance Dosage:

1. Wash and dry your hands before handling the IMVEXXY insert.
2. Place one vaginal insert into your vagina, twice a week (every three to four days).
3. Write down the days you will put in your IMVEXXY insert.

- Your healthcare professional may interrupt or stop your treatment with IMVEXXY. This will depend on your condition and how you are feeling.

Overdose:

Signs of an overdose may include feeling sick or vomiting, breast pain, fluid retention (swelling), or bloating. Vaginal bleeding might occur as well.

If you think you, or a person you are caring for, have taken too much IMVEXXY contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to use a vaginal insert, use one as soon as you remember. However, if the dose is close to the next scheduled dose, skip the missed insert and continue with your next scheduled insert.

Do not use two vaginal inserts to make up for a missed dose.

What are possible side effects from using IMVEXXY?

These are not all the possible side effects you may have when taking IMVEXXY. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- Headache, dizziness, memory loss
- Vision changes
- Abdominal, back and pelvic pain
- Nausea
- Diarrhea
- Feeling bloated
- Feeling tired (fatigue)
- Change in appetite, body weight
- Excessive sweating, body odor
- Vaginal discharge, discomfort, odor
- Anxiety, feeling nervous
- Loss of scalp hair
- Excess hair on face, chest, abdomen or legs
- Breast tenderness, pain, swelling
- Acne, rash, itchy skin
- Pain during sex

IMVEXXY can cause abnormal blood test results. Your healthcare professional will decide when these are necessary and will interpret the results. They will tell you if your test results are abnormal and if you need treatment.

The risks related to oral estrogen should be considered as well. Serious side effects that are possible with IMVEXXY, as well as oral estrogen, are listed in the table below.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON			
Nasopharyngitis (a cold): runny or stuffy nose, sore throat, cough, sinus congestion, body aches, headache, sneezing, fever, generally feeling unwell	**√**		

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Urinary tract infection (infection in urinary system including kidneys, ureters, bladder and urethra): pain or burning sensation while urinating, frequent urination, blood in urine, pain in the pelvis, strong smelling urine, cloudy urine		**√**	
Vaginal bleeding changes: increased or decreased menstrual bleeding, spotting, infrequent periods or absence of bleeding, severe vaginal bleeding		**√**	
UNCOMMON			
Stroke (blood clot in the brain): sudden severe headache, vomiting, dizziness, fainting, problems with your vision or speech, weakness or numbness in the face, arm, or leg			**√**
Pulmonary embolism (blood clot in the lungs): sharp chest pain, coughing up blood, or sudden shortness of breath			**√**
Deep vein thrombosis (blood clot in the legs) **or Thrombophlebitis** (inflammation of a vein often in the leg): sudden leg swelling or pain; redness, warmth, tenderness and pain in affected area			**√**
RARE			
Breast abnormalities (including breast cancer): dimpling or sinking of the skin, changes in the nipple, or any lumps you can see or feel, discharge from breasts, enlarged breasts, swelling			**√**
Coronary thrombosis (blocked heart arteries): chest pain and pressure, shortness of breath			**√**
Cystitis (bladder infection): increased need to urinate, pain in the pelvis or lower back, frequent urination during the night, cloudy urine that may contain blood, burning sensation when passing urine		**√**	
Depression (sad mood that won't go away): difficulty sleeping or sleeping too much, changes in appetite or weight, feelings of worthlessness, guilt, regret, helplessness or hopelessness, withdrawal from social situations, family, gatherings and		**√**	

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
activities with friends, reduced libido (sex drive) and thoughts of death or suicide.			
Endometrial hyperplasia (abnormal growth of the lining of the uterus)**:** menstrual bleeding that is heavier or lasts longer than normal, bleeding after menopause, menstrual cycles that are shorter than 21 days			**√**
Endometrial cancer (cancer of the lining of the uterus): vaginal bleeding not associated with a period or after menopause; abnormal blood-tinged discharge from the vagina; pain in the pelvis			**√**
Erythema multiforme (an allergic skin reaction): raised red or purple skin patches, possibly with blister or crust in the center; possibly swollen lips, mild itching or burning			**√**
Erythema nodosum (swelling of the fat cells under the skin): tender red lumps usually on both shins			**√**
Eye disorders: blurred vision, loss of vision in eye, increased sensitivity of the eyes to light, eye pain or redness, swelling and itching of the eyelids, decreased sharpness of vision, eye irritation, blocked eye veins		**√**	
Gastrointestinal disorders: stomach pain, decreased appetite, diarrhea, nausea, vomiting, vomiting of blood, black stools, constipation, heartburn, swelling or bloating of the abdomen, blood in stool		**√**	
Hypertension (high blood pressure): shortness of breath, fatigue, dizziness or fainting, chest pain or pressure, swelling in your ankles and legs, bluish colour to your lips and skin, racing pulse or heart palpitations		**√**	
Liver problems: yellowing of your skin and eyes (jaundice), right upper stomach area pain or swelling, nausea or vomiting, unusual dark urine, light coloured stool, unusual tiredness		**√**	
Migraine: severe headache often accompanied by nausea, vomiting and sensitivity to light	**√**		

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Neuritis (inflammation of a nerve): pain, feeling of pins-and needles, numbness, loss of reflexes		**√**	
Ovarian cancer: abdominal pain or bloating, quickly feeling full after eating, weight loss, pain in pelvis, change in bowel habits, need to urinate often			**√**
Palpitation (fast-beating, fluttering or pounding heart): skipping beats, beating too fast, pounding, fluttering rapidly			**√**
Peripheral edema (swelling of the legs or hands caused by fluid retention): swollen or puffy legs or hands, feeling heavy, achy or stiff		**√**	
Urinary tract disorders: difficulty and pain when passing urine, blood in urine		**√**	
Vaginal yeast infection (inflammation of the vagina): itching, burning, or discharge from the vagina			**√**
Gallbladder problems: fever, nausea, pain that radiates to your shoulder or back, severe pain in your upper right abdomen, vomiting	**√**		
Hypersensitivity (allergic reaction): fever, skin rash, hives, itching, swelling, shortness of breath, wheezing, runny nose, itchy, watery eyes			**√**
Dementia (memory and thinking problems): memory loss, impaired thinking, difficulty speaking, loss of control of body movements, disorientation, trembling		**√**	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store IMVEXXY at room temperature between 15°C and 25°C.
- Keep out of reach and sight of children.

If you want more information about IMVEXXY

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp); the manufacturer's website (https://knighttx.com), by emailing medinfo@knighttx.com, or by calling 1-844-483-5636.

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