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Press Release

Hikma launches Estradiol Valerate Injection, USP

London, 2 June, 2021 – Hikma Pharmaceuticals PLC (Hikma), the multinational pharmaceutical company, has launched Estradiol Valerate Injection, USP 10mg/mL, 20mg/mL and 40mg/mL in the US, through its US affiliate, Hikma Pharmaceuticals USA Inc.

Estradiol Valerate Injection, USP is indicated: (i) in the treatment of vasomotor symptoms associated with menopause; (ii) in the management of hormonal imbalances due to castration or primary ovarian failure; and (iii) in the treatment of androgen-dependent carcinoma of the prostate.

According to IQVIA, US sales of Estradiol Valerate Injection, USP 10mg/mL, 20mg/mL and 40mg/mL were approximately $16 million in the 12 months ending March 2021.

Hikma is the third largest US supplier of generic injectable medicines by volume, with a growing portfolio of over 100 products. Today one in every six injectable generic medicines used in US hospitals is a Hikma product.

- ENDS -

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About Hikma
(LSE: HIK) (NASDAQ Dubai: HIK) (OTC: HKMPY) (rated BBB-/stable S&P and BBB-/stable Fitch)

Hikma helps put better health within reach every day for millions of people around the world. For more than 40 years, we've been creating high-quality medicines and making them accessible to the people who need them. Headquartered in the UK, we are a global company with a local presence across the United States (US), the Middle East and North Africa (MENA) and Europe, and we use our unique insight and expertise to transform cutting-edge science into innovative solutions that transform people's lives. We're committed to our customers, and the people they care for, and by thinking creatively and acting practically, we provide them with a broad range of branded and non-branded generic medicines. Together, our 8,600 colleagues are helping to shape a healthier world that enriches all our communities. We are a leading licensing partner, and through our venture capital arm, are helping bring innovative health technologies to people around the world. For more information, please visit: www.hikma.com

Important Safety Information for Estradiol Valerate Injection, USP 10mg/mL, 20mg/mL and 40mg/mL:

BOXED WARNING

ESTROGENS INCREASE THE RISK OF ENDOMETRIAL CANCER
Close clinical surveillance of all women taking estrogens is important. Adequate diagnostic measures, including endometrial sampling when indicated, should be undertaken to rule out malignancy in all cases of undiagnosed persistent or recurring abnormal vaginal bleeding. There is no evidence that the use of "natural" estrogens results in a different endometrial risk profile than synthetic estrogens at equivalent estrogen doses. (See **WARNINGS, Malignant neoplasms, Endometrial cancer.**)

CARDIOVASCULAR AND OTHER RISKS
Estrogens and progestins should not be used for the prevention of cardiovascular disease. (See **WARNINGS, Cardiovascular disorders.**)

The Women's Health Initiative (WHI) study reported increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary emboli, and deep vein thrombosis in postmenopausal women (50 to 79 years of age) during 5 years of treatment with oral conjugated estrogens (CE 0.625 mg) combined with medroxyprogesterone acetate (MPA 2.5 mg) relative to placebo. (See **CLINICAL PHARMACOLOGY, Clinical Studies.**)

The Women's Health Initiative Memory Study (WHIMS), a substudy of WHI, reported increased risk of developing probable dementia in postmenopausal women 65 years of age or older during 4 years of treatment with oral conjugated estrogens plus medroxyprogesterone acetate relative to placebo. It is unknown whether this finding applies to younger postmenopausal women or to women taking estrogen alone therapy. (See **CLINICAL PHARMACOLOGY, Clinical Studies.**)

Other doses of oral conjugated estrogens with medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestins were not studied in the WHI clinical trials and, in the absence of comparable data, these risks should be assumed to be similar. Because of these risks, estrogens with or without progestins should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual woman.

CONTRAINDICATIONS

Estradiol Valerate Injection should not be used in women with any of the following conditions:
1 Undiagnosed abnormal genital bleeding.
2 Known, suspected, or history of cancer of the breast.
3 Known or suspected estrogen-dependent neoplasia.
4 Active deep vein thrombosis, pulmonary embolism or a history of these conditions.
5 Active or recent (e.g., within the past year) arterial thromboembolic disease (e.g., stroke, myocardial infarction).
6 Liver dysfunction or disease.
7 Estradiol Valerate Injection should not be used in patients with known hypersensitivity to its ingredients.
8 Known or suspected pregnancy. There is no indication for Estradiol Valerate Injection in pregnancy. There appears to be little or no increased risk of birth defects in children born to women who have used estrogens and progestins from oral contraceptives inadvertently during early pregnancy. (See **PRECAUTIONS**.)

WARNINGS & PRECAUTIONS

- Estrogen and estrogen/progestin therapy has been associated with an increased risk of cardiovascular events such as myocardial infarction and stroke, as well as venous thrombosis and pulmonary embolism (venous thromboembolism or VTE).
- Large doses of estrogen (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risks of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis.
- If feasible, estrogens should be discontinued at least 4 to 6 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization.
- The use of unopposed estrogens in women with intact uteri has been associated with an increased risk of endometrial cancer.
- The use of estrogens and progestins by postmenopausal women has been reported to increase the risk of breast cancer. The addition of a progestin when a woman has not had a hysterectomy has a possible increased risk of breast cancer.
- The CE/MPa sub-study of WHI reported that estrogen plus progestin increased the risk of ovarian cancer.
- In the Women's Health Initiative Memory Study, women treated with conjugated estrogens plus medroxyprogesterone acetate were reported to have a two-fold increase in the risk of developing probable

dementia. Alzheimer's disease was the most common classification of probable dementia.

- A 2-to 4-fold increase in the risk of gallbladder disease requiring surgery in postmenopausal women receiving estrogens has been reported.
- Estrogen administration may lead to severe hypercalcemia in patients with breast cancer and bone metastases.
- Retinal vascular thrombosis has been reported in patients receiving estrogens.
- In a small number of case reports, substantial increases in blood pressure have been attributed to idiosyncratic reactions to estrogens.
- In patients with pre-existing hypertriglyceridemia, estrogen therapy may be associated with elevations of plasma triglycerides leading to pancreatitis and other complications.
- Estrogens may be poorly metabolized in patients with impaired liver function.
- Estrogen administration leads to increased thyroid-binding globulin (TBG) levels.
- Because estrogens may cause some degree of fluid retention, patients with conditions that might be influenced by this factor, such as a cardiac or renal dysfunction, warrant careful observation when estrogens are prescribed.
- Estrogens should be used with caution in individuals with severe hypocalcemia.
- Endometriosis may be exacerbated with administration of estrogens.
- Estrogens may cause an exacerbation of asthma, diabetes mellitus, epilepsy, migraine or porphyria, systemic lupus erythematosus, and hepatic hemangiomas and should be used with caution in women with these conditions.
- Some studies have shown that women taking estrogen replacement therapy have hypercoagulability, primarily related to decreased antithrombin activity.
- Certain patients may develop undesirable manifestations of estrogenic stimulation, such as abnormal uterine bleeding and mastodynia.
- Estrogen administration should be initiated at the lowest dose approved for the indication and then guided by clinical response rather than by serum hormone levels (e.g., estradiol, FSH).
- Refer to package insert for Drug/Laboratory Test Interactions.

ADVERSE REACTIONS

The following adverse reactions have been reported with estrogen and/or progestin therapy.

Genitourinary system: changes in vaginal bleeding pattern and abnormal withdrawal bleeding or flow; breakthrough bleeding; spotting; dysmenorrhea, increase in size of uterine leiomyomata; vaginitis, including vaginal candidiasis; change in amount of cervical secretion; changes in cervical ectropion; ovarian cancer; endometrial hyperplasia; endometrial cancer.

Breasts: tenderness, enlargement, pain, nipple discharge, galactorrhea; fibrocystic breast changes; breast cancer.

Cardiovascular: deep and superficial venous thrombosis; pulmonary embolism; thrombophlebitis; myocardial infarction; stroke; increase in blood pressure.

Gastrointestinal: nausea, vomiting; abdominal cramps, bloating; cholestatic jaundice; increased incidence of gallbladder disease; pancreatitis, enlargement of hepatic hemangiomas.

Skin: chloasma or melasma, which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism; pruritus, rash.

Eyes: retinal vascular thrombosis; intolerance to contact lenses.

Central Nervous System: headache; migraine; dizziness; mental depression; chorea; nervousness; mood disturbances; irritability; exacerbation of epilepsy, dementia.

Miscellaneous: increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; arthalgias; leg cramps; changes in libido; urticaria, angioedema, anaphylactoid/anaphylactic reactions; hypocalcemia; exacerbation of asthma; increased triglycerides.

DRUG INTERACTIONS

In vitro and *in vivo* studies have shown that estrogens are metabolized partially by cytochrome P450 3A4 (CYP3A4). Therefore, inducers or inhibitors of CYP3A4 may affect estrogen drug metabolism. Inducers of CYP3A4

such as St. John's Wort preparations (Hypericum perforatum), phenobarbital, carbamazepine, and rifampin may reduce plasma concentrations of estrogens, possibly resulting in a decrease in therapeutic effects and/or changes in the uterine bleeding profile. Inhibitors of CYP3A4 such as erythromycin, clarithromycin, ketoconazole, itraconazole, ritonavir and grapefruit juice may increase plasma concentrations of estrogens and may result in side effects.

USE IN SPECIFIC POPULATIONS

Carcinogenesis, Mutagenesis, and Impairment of Fertility
Long-term continuous administration of estrogen, with and without progestin, in women with and without a uterus, has shown an increased risk of endometrial cancer, breast cancer, and ovarian cancer.

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.

Pregnancy
Estradiol Valerate Injection should not be used during pregnancy.

Nursing Mothers
Estrogen administration to nursing mothers has been shown to decrease the quantity and quality of the milk. Detectable amounts of estrogens have been identified in the milk of mothers receiving this drug. Caution should be exercised when Estradiol Valerate Injection is administered to a nursing woman.

Pediatric Use
Safety and effectiveness in pediatric patients have not been established. Large and repeated doses of estrogen over an extended period of time may accelerate epiphyseal closure. Therefore, periodic monitoring of bone maturation and effects on epiphyseal centers is recommended in patients in whom bone growth is not complete.

Geriatric Use
Clinical studies of estradiol valerate did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

In the Women's Health Initiative Memory Study, including 4,532 women 65 years of age and older, followed for an average of 4 years, 82% (n = 3,729) were 65 to 74 while 18% (n = 803) were 75 and over. Most women (80%) had no prior hormone therapy use. Women treated with conjugated estrogens plus medroxyprogesterone acetate were reported to have a two-fold increase in the risk of developing probable dementia. Alzheimer's disease was the most common classification of probable dementia in both the conjugated estrogens plus medroxyprogesterone acetate group and the placebo group. Ninety percent of the cases of probable dementia occurred in the 54% of the women that were older than 70. It is unknown whether these findings apply to estrogen alone therapy.

DOSAGE AND ADMINISTRATION

When estrogen is prescribed for a postmenopausal woman with a uterus, progestin should also be initiated to reduce the risk of endometrial cancer. A woman without a uterus does not need progestin. Use of estrogen, alone or in combination with a progestin, should be with the lowest effective dose and for the shortest duration consistent with treatment goals and risks for the individual woman.

Care should be taken to inject deeply into the upper, outer quadrant of the gluteal muscle following the usual precautions for intramuscular administration. By virtue of the low viscosity of the vehicles,
the various preparations of Estradiol Valerate Injection, may be administered with a small gauge needle (i.e., 20 Gauge × 1 ½ inches long). Since the 40 mg potency provides a high concentration in a small volume, particular care should be observed to administer the full dose.

Estradiol Valerate Injection should be visually inspected for particulate matter and color prior to administration; the solution is clear, colorless to pale yellow. Storage at low temperatures may result in the separation of some crystalline material which redissolves readily on warming.

Refer to the package insert for usual dosage recommendations for treatment of 1) moderate to severe vasomotor symptoms, vulvar and vaginal atrophy associated with the menopause, 2) female hypoestrogenism due to

hypogonadism, castration, or primary ovarian failure, and 3) advanced androgen-dependent carcinoma of the prostate, for palliation only.

Overdosage

Serious ill effects have not been reported following acute ingestion of large doses of estrogen-containing drug products by young children. Overdosage of estrogen may cause nausea and vomiting, and withdrawal bleeding may occur in females.

INDICATIONS

Estradiol Valerate Injection, USP is indicated in the:
1. Treatment of moderate to severe vasomotor symptoms associated with the menopause.
2. Treatment of moderate to severe symptoms of vulvar and vaginal atrophy associated with the menopause. When prescribing solely for the treatment of symptoms of vulvar and vaginal atrophy, topical vaginal products should be considered.
3. Treatment of hypoestrogenism due to hypogonadism, castration or primary ovarian failure.
4. Treatment of advanced androgen-dependent carcinoma of the prostate (for palliation only).

ENDING INFORMATION

Patient Counseling Information should be shared with the patient prior to administration.
For additional information, please refer to the Package Insert for full prescribing information, available on www.hikma.com.

For medical advice about adverse reactions contact your medical professional. To report SUSPECTED ADVERSE REACTIONS, contact Hikma Pharmaceuticals USA Inc. at 1-877-233-2001 or the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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