DIVIGEL 0.1 % GEL

Qualitative and quantitative composition

Active ingredient and excipients
Estradiol hemihydrate corresponding to 1.0 mg estradiol/dose (in single dose units containing 1.0 g gel).
Estradiol hemihydrate corresponding to 0.5 mg estradiol/dose (in single dose units containing 0.5 g gel).
Carbomer 974P, Trolamine, Propylene Glycol, Ethanol, Aq. Purif.

Pharmaceutical Forms
Smooth and opalescent gel

Clinical particulars

Therapeutic Indications
Treatment of the climacteric syndrome associated with natural or artificial menopause (estrogenic deficiency, e.g. hot flushes, night sweatings, urogenital atrophy and prevention of postmenopausal (type 1) osteoporosis).

Dosage and Administration
Divigel can be used for continuous or cyclical treatment. The dose can be adjusted individually from 0.5 g to 1.5 g per day, corresponding to 0.5 to 1.5 mg estradiol per day. The usual starting dose is 1.0 mg estradiol (1.0 g gel) daily and can be readjusted after 2 to 3 cycles.
In patients with an intact uterus, it is recommended to combine Divigel with an adequate dose of progestin for adequate duration, e.g. 12-14 consecutive days per cycle.
Estrogen with or without progestogens should be prescribed at the lowest effective doses and for the shortest duration consistent with treatment goals and risks for the individual women.
The Divigel dose is applied once daily, on the skin of the lower trunk or the right or left thighs, on alternate days. The application surface should be 1-2 times the size of the hand. Divigel should not be applied on the breasts, on the face or irritated skin. After application the gel should be allowed to dry for a few minutes and the application site should not be washed within one hour. Accidental contact of the gel with the eyes should be avoided. Hands should be washed after application.
If the patient forgets to apply a dose, it should be applied as soon as possible, unless the dose is more than 12 hours late. If the dose is more than 12 hours late, it should be skipped. Missed doses may induce breakthrough bleeding.

Route of Administration
For topical use only

Contraindications
Undiagnosed vaginal bleeding. Confirmed active venous thromboembolism (deep venous thrombosis (DVT), pulmonary embolism) within the last 2 years. A history of recurrent venous thromboembolism (VTE) or known thrombophilic disease in a patient who is not lately on anticoagulant treatment (See Special warnings and special precautions for use). Severe hepatic disease (including Dubin-Johnson and Rotor's syndrome). Known or suspected malignant conditions, especially breast cancer and/or endometrial cancer, if sex steroid influenced. Hypersensitivity to the constituents of the preparation.

Special Warnings and Special Precautions for Use
Before therapy is initiated, a thorough medical history should be taken. A complete gynecological examination should be performed and repeated at least once a year during therapy. Follow-up examination of the breasts and/or mammography should be carried out in accordance with current acceptance practices, modified according to the clinical needs of the individual.
Prolonged use without addition of a progestin may cause endometrial hyperplasia. Therefore, in women with an intact uterus, Divigel treatment should be combined with cyclic progestin administration. Withdrawal bleeding resembling normal menstruation will usually occur after each course of progestin. The cause of unexpected or prolonged uterine bleeding during therapy should be clarified. Atypical adenomatous hyperplasia of endometrium must be treated before entering estrogen therapy.
Development of de novo frequent severe headaches or migraine should be investigated and possible prodromal symptoms of vascular occlusion should be clarified.
The risks and benefits of treatment should be evaluated and close monitoring performed for patients with:
Endometriosis. Uterine leiomyoma. Endometrial hyperplasia (simple glandular hyperplasia or hyperplasia glandularis cystica). Diseases of the cardiovascular system including cerebrovascular disorders. History of thromboembolic disease. Severe hypertension. History of (or close family history of) breast cancer. Severe disturbances of the lipid metabolism. Renal dysfunction. Systemic lupus erythematosus. Porphyria.
A reanalysis of original data from 51 epidemiological studies reported a small or moderate increase in the probability of having breast cancer diagnosed in women currently or recently using HRT. The findings may be due to an earlier diagnosis, the biological effects of HRT, or a combination of both. The probability of diagnosing breast cancer increased with duration of treatment: breast cancers diagnosed in current or recent users of HRT are less likely to have spread outside the breast than those found in non-users.
Results from a large meta-analysis showed that after stopping treatment, the excess risk will decrease with time and the time needed to return to baseline depends on the duration of prior HRT use. When HRT was taken for more than 5 years, the risk may persist for 10 years or more. Between the ages of 50- 70 years, about 45 women in every 1000 not using HRT will have breast cancer diagnosed, the rate increasing with age. It is estimated that among those who use HRT for 5 to 15 years, depending on the age of starting and duration of treatment, the number of additional cases of breast cancer diagnosed will be of the order of 2 to 12 cases per 1000 women.
Ovarian Cancer: Ovarian cancer is much rarer than breast cancer. Epidemiological evidence from a large meta-analysis suggests a slightly increased risk in women taking oestrogen-only or combined oestrogen-progestagen HRT, which becomes apparent within 5 years of use and diminishes over time after stopping. Some other studies, including the Women's Health Initiative trial, suggest that the use of combined HRTs may be associated with a similar or slightly smaller risk.
Epidemiological studies have suggested that HRT is associated with a higher relative risk of developing venous VTE, i.e. DVT or pulmonary emboilism. The studies find a 2 – 3 fold higher risk for users compared with non-users, which for healthy women amounts to one to two additional cases of VTE in 10,000 patient-years of treatment with HRT. The occurrence of such an event is more likely in the first year of HRT than later.
Generally recognised risk factors for VTE include a personal history or family history, severe obesity (Body Mass Index > 30 kg/m^2) and systemic lupus erythematosus (SLE). There is no consensus about the possible role of vericose veins in VTE.
Use of HRT in patients with a history of recurrent VTE or known thrombophilic states already on anticoagulant treatment require careful consideration of the benefit-risk of use of HRT (see also Contraindications).
The presence of a personal or strong family history of recurrent thromboembolism or recurrent spontaneous abortion should be investigated in order to exclude a thrombophilic predisposition. Until a definitive diagnosis has been made or anticoagulant treatment initiated, use of HRT in such patients should be viewed as contra-indicated.
The risk of VTE may be temporarily increased with prolonged immobilisation, major trauma or major surgery. As in all post-operative patients, scrupulous attention should be given to prophylactic measures to prevent VTE following surgery. Where prolonged immobilisation is liable to follow elective surgery, particularly abdominal or orthopaedic surgery to the lower limbs, consideration should be given to temporarily stopping HRT four to six weeks earlier, if possible.
If VTE develops after initiating therapy, Divigel should be discontinued.
Patients should be told to contact their doctors immediately when they are aware of a potential thromboembolic symptom (e.g. painful swelling of a leg, sudden pain in the chest, dyspepsia).

Some conditions may be aggravated during estrogen therapy or pregnancy. Women on Divigel treatment with one of the following conditions (or with a history thereof during previous pregnancy or hormone use) should therefore be closely monitored. These conditions include:
Mild hypertension. Migraine or severe headache. Benign breast disease. Liver function disturbances. Cholestasis. Cholelithiasis. Diabetes mellitus. Asthma. Otosclerosis. Multiple sclerosis. Galactorrhea, elevated prolactin levels. History of herpes gestationis. Epilepsy.

Interactions with other medications
No interactions between Divigel and other medicines have been reported.
There are some indications that estrogens may reduce the effects of antihypertensive, anticoagulant and antidiabetic drugs. Concomitant treatment with potent inducers of liver enzymes (e.g. barbiturates, carbamazepine, griseofulvin and rifampicin) may reduce the plasma levels of estradiol. The significance of these interactions in transdermal application has not been elucidated.

Use in Pregnancy and Lactation:
Divigel is not indicated in women of child-bearing potential. It has no contraceptive efficacy. Divigel should not be used during pregnancy or lactation.

Effect on ability to drive and use machines
Estrogens such as Divigel do not affect the ability to drive or use machines.

Adverse Reactions
Adverse drug reactions reported during clinical trials with Divigel and estrogen replacement therapy are usually mild and only seldom lead to discontinuation of the treatment. If they do occur, it will usually be during the first months of the treatment.
Very common (> 1/10) :
Reproductive: Breast tenderness
Common (> 1/100, < 1/10) :
Central nervous system: Headache
Metabolic and nutritional: Oedema, weight increase
Reproductive: Unscheduled vaginal bleeding or spotting
Gastrointestinal: Nausea, vomiting, stomach cramps
Application site: Skin irritation
Rare (> 1/10,000, < 1/1,000) :
Ovarian Cancer: Use of oestrogen-only or combined oestrogen-progestagen HRT has been associated with a slightly increased risk of having ovarian cancer diagnosed.
A meta-analysis from 52 epidemiological studies reported an increased risk of ovarian cancer in women currently using HRT compared to women who have never used HRT (RR 1.43, 95% CI 1.31-1.56). For women aged 50 to 54 years taking 5 years of HRT, this results in about 1 extra case per 2000 users. In women aged 50 to 54 who are not taking HRT, about 2 women in 2000 will be diagnosed with ovarian cancer over a 5-year period.
Central nervous system: Migraine
Psychic: Changes in libido and mood
Cardiovascular: Venous thromboembolism
Very rare (< 1/10,000), including isolated reports :
Cardiovascular: Hypertension
Hepato-biliary: Alterations in liver function and biliary flow
Skin and subcutaneous tissue: Rash

Overdose and Treatment
Generally, estrogens are well tolerated even in massive doses. Possible symptoms of overdose include those listed under undesirable effects. Treatment is symptomatic.

Pharmacological properties

Pharmacodynamic properties:
The Pharmacodynamics of Divigel are similar to those of oral estrogens, but the major difference to oral administration lies in the pharmacokinetic profile. The clinical efficacy of Divigel in the treatment of menopausal symptoms is comparable to that of peroral estrogen. Combined with medroxyprogesterone acetate, percutaneous estradiol treatment lowers total cholesterol without reducing the HDL cholesterol level.

Pharmacokinetic properties
Divigel is an alcohol-based estradiol gel. When applied to the skin the alcohol evaporates rapidly and estradiol is absorbed through the skin into the circulation. To some extent, however, the estradiol is stored in subcutaneous tissue from where it is released gradually into circulation. Percutaneous administration circumvents the hepatic first-pass metabolism. For these reasons, the fluctuations in the plasma estrogen concentrations with Divigel are less pronounced than with peroral estrogen.
A 1.5 mg percutaneous dose of estradiol (1.5 g Divigel) results in a plasma concentration of about 340 pmol/l, which corresponds to the level of early follicular stage in premenopausal women. During Divigel treatment the estradiol/estrone ratio remains at 0.7, while during peroral estrogen treatment it usually drops to less than 0.2. The mean estradiol at steady state of Divigel is 82 per cent compared with an equivalent oral dose of estradiol valerate. Otherwise the metabolism and excretion of transdermal estradiol follow the fate of natural estrogens.

Preclinical safety data
Estradiol is a natural female hormone with an established clinical use, therefore no toxicological studies have been performed with Divigel. The necessary studies on the irritant effects of the gel have been studied in rabbits and skin sensitisation in guinea pig. Based on the results from these studies it can be concluded that Divigel very infrequently could cause mild skin irritation. The frequency of the occurrence of dermal irritation can be reduced by daily change of the application site.

Pharmaceutical particulars

Incompatibilities
No incompatibilities have been found

Presentations
Divigel 0.1 % Gel is available in either 0.5 g or 1.0 g single-dose aluminium foil sachets, supplied in packages containing 7 or 28 or 91 sachets of either dose. Not all pack sizes may be marketed.

Special precautions for storage:
Store below 30°C.
Keep out of reach of children.
See the package for the expiry date.
Do not use the medicine after the stated date.

Manufactured by:
Orion Corporation
Orion Pharma
Tengströminkatu 8
Turku, FI-20360
Finland

Product registration holder:
Orion Pharma (MY) Sdn. Bhd.
E-20-01, Menara SUEZCAP 2,
KL Gateway, No. 2, Jalan Kerinchi,
Gerbang Kerinchi Lestari,
59200 Kuala Lumpur,
Malaysia

Product registrant:
Orion Pharma (SG) Pte. Ltd.

Date of revision: Mar 2022

ORION PHARMA