PRESCRIBING INFORMATION:

Divigel 1.0 mg Gel (Estradiol hemihydrate)

Indication: Hormone Replacement Therapy (HRT) for oestrogen deficiency symptoms in postmenopausal women. Experience in women more than 65 years old is limited.

Dosage and Administration: Divigel is a gel for transdermal use and can be used for continuous or cyclical treatment. The usual starting dose is 1.0 mg estradiol (1.0 g gel) daily but the selection of the initial dose can be based on the severity of the patient' s symptoms. Depending on the clinical response, the dosage can be readjusted after 2-3 cycles individually from 0.5 g to 1.5 g per day, corresponding to 0.5 to 1.5 mg estradiol per day. For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration should be used. In patients with an intact uterus, it is recommended to combine Divigel with an adequate dose of progestagen, for adequate duration for at least 12-14 consecutive days per month/28 day cycle or to oppose oestrogen-stimulated hyperplasia of the endometrium. Unless there is a previous diagnosis of endometriosis, it is not recommended to add a progestagen in hysterectomised women. Apply on dry and clean skin once daily on the skin of the lower trunk of the right or left thigh, on alternate days. The application surface should be 1-2 times the size of a 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 1 hour. Contact of the gel with eyes should be avoided. Unintended exposure of another person through skin contact should be avoided, see full SmPC for details. Hands should be washed after application.

Contraindications: Known, past or suspected breast cancer; known or suspected oestrogen-dependent malignant tumours; undiagnosed genital bleeding; untreated endometrial hyperplasia; previous or current venous thromboembolism (deep venous thrombosis, pulmonary embolism); known thrombophilic disorders (e.g., protein C, protein S or antithrombin deficiency), active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction); acute liver disease or a history of liver disease as long as liver function tests have failed to return to normal; known hypersensitivity to the active substances or to any of the excipients; porphyria.

Warnings and Precautions: For the treatment of postmenopausal symptoms, HRT should only be initiated for symptoms that adversely affect quality of life. In all cases, a careful appraisal of the risks and benefits should be undertaken at least annually, and HRT should only be continued as long as the benefit outweighs the risk. Evidence regarding the risks associated with HRT in the treatment of premature menopause is limited. Due to the low level of absolute risk in younger womena however, the balance of benefits and risks for these women may be more favourable than in older women. Medical Examination: before initiating or reinstituting HRT, a complete personal and family medical history should be taken. Physical (including pelvic and breast) examination should be guided by this and by the contraindications and warnings for use. During treatment, periodic check-ups are recommended of a frequency and nature adapted to the individual woman. Women should be advised what changes in their breasts should be reported to their doctor or nurse. Investigations, including appropriate imaging tools should be carried out in accordance with currently accepted screening practices, modified to the clinical needs of the individual. Conditions which need supervision: if any of the following conditions are present, have occurred previously and/or have been aggravated during pregnancy or previous hormone treatment, the patient should be closely supervised. It should be taken into account that these conditions may recur or be aggravated during treatment, in particular: leiomyoma (uterine fibroids) or endometriosis, risk factors for thromboembolic disorders, risk factors for oestrogen dependent tumours, hypertension, liver disorders (e.g., liver adenoma), diabetes mellitus with or without vascular involvement, cholelithiasis, migraine or (severe) headache, systemic lupus erythematosus, history of endometrial hyperplasia, epilepsy, asthma, otosclerosis, hereditary angioedema. Reasons for immediate withdrawal of therapy: discontinue if a contraindication is discovered and in the following situations: jaundice or deterioration in liver function, significant increase in blood pressure, new onset of migraine-type headache, pregnancy. Endometrial hyperplasia and carcinoma: In women with an intact uterus the risk of endometrial hyperplasia and carcinoma is increased when oestrogens are administered alone for prolonged periods. The reported increase in endometrial cancer risk among oestrogen-only users varies from 2-to 12-fold greater compared with non-users, depending on the duration of treatment and oestrogen dose. After stopping treatment risk may remain elevated for at least 10 years. The addition of a progestagen cyclically for at least 12 days per month/28 day cycle or continuous combined oestrogen-progestagen therapy in non-hysterectomised women prevents the excess risk associated with oestrogen-only HRT. Breakthrough bleeding and spotting may occur during the first months of treatment. If breakthrough bleeding or spotting appears after some time on therapy, or continues after treatment has been discontinued, the reason should be investigated. Unopposed oestrogen stimulation may lead to premalignant or malignant transformation in the residual foci of endometriosis. Therefore, the addition of progestagens to oestrogen replacement therapy should be considered in women who have undergone hysterectomy because of endometriosis, if they are known to have residual endometriosis Breast cancer: Evidence suggests an increased risk of breast cancer in women taking combined oestrogen-progestagen or oestrogen-only HRT, that is dependent on the duration of taking HRT. *Combined oestrogen-progestagen therapy* - the Women' s Health Initiative study (WHI) and a meta-analysis of prospective epidemiological studies are consistent in finding an increased risk of breast cancer in women taking combined oestrogen-progestagen for HRT that becomes apparent after about 3 years (1-4). *Oestrogen-only therapy* - the WHI trial found no increase in the risk of breast cancer in hysterectomised women using oestrogen-only HRT. Observational studies have mostly reported a small increase in risk of having breast cancer diagnosed that is substantially lower than that found in users of oestrogen-progestagen combinations. 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. HRT, especially oestrogen-progestagen combined treatment, increases the density of mammographic images which may adversely affect the radiological detection of breast cancer. Ovarian cancer: Ovarian cancer is much rarer than breast cancer. Epidemiological evidence 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. Other studies, including the WHI trial, suggest that use of combined HRTs may be associated with a similar or slightly smaller risk. Venous thromboembolism (VTE): HRT is associated with a 1.3-3 fold risk of developing VTE i.e. deep vein thrombosis or pulmonary embolism. Patients with a history of VTE or known thrombophilic states have an increased risk of VTE and HRT may add to this risk. HRT is therefore contraindicated. Generally recognised risk factors for VTE include, use of oestrogens, older age, major surgery, prolonged immobilisation, obesity (BMI > 30 kg/m2), pregnancy/postpartum period, systemic lupus erythematosus and cancer. Consider prophylactic measures to prevent VTE following surgery. If prolonged immobilisation is to follow elective surgery temporarily, stop HRT 4 to 6 weeks earlier. Restart when women is completely mobilised. Screen women with a first degree relative with a history of thrombosis at young age. If a thrombophilic defect is identified which segregates with thrombosis in family members or if the defect is 'severe' , HRT is contraindicated. Women already on chronic anticoagulant treatment require careful consideration of the benefit-risk of use of HRT. If VTE develops after initiating therapy, the drug should be discontinued. Patients should be told to contact their doctors immediately when they are aware of a potential thromboembolic symptom. Coronary artery disease (CAD): There is no evidence from randomised controlled trials of protection against myocardial infarction in women with or without existing CAD who received combined oestrogen-progestagen or oestrogen-only HRT. Combined oestrogen-progestagen therapy: the relative risk of CAD during use of combined oestrogen+progestagen HRT is slightly increased. *Oestrogen-only:* randomised controlled data found no increased risk of CAD in hysterectomised women using oestrogen-only therapy. Ischaemic stroke: Combined oestrogen-progestagen and oestrogen-only therapy are associated with an up to 1.5-fold increase in risk of ischaemic stroke. The relative risk does not change with age or time since menopause. However, as the baseline risk of stroke is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age. Other conditions: Oestrogens may cause fluid retention so patients with cardiac or renal dysfunction should be carefully observed. Women with pre-existing hypertriglyceridemia should be followed closely, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with oestrogen therapy in this condition. Exogenous estrogens may induce or exacerbate symptoms of hereditary and acquired angioedema. Oestrogens increase thyroid binding globulin, leading to increased circulating total thyroid hormone. Other binding proteins may be elevated in serum, i.e., corticoid binding globulin, sex-hormone-binding globulin leading o increased circulating corticosteroids and sex steroids, respectively. Free or biological active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin). Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. HRT use does not improve cognitive function. There is some evidence of increased risk of probable dementia in women who start using continuous combined or oestrogen-only HRT after the age of 65. Potential estradiol transfer to children: estradiol gel can be accidentally transferred to children from the area of the skin where it was applied on. Breast budding and breast masses in prepubertal females, precocious puberty, gynaecomastia and breast masses in prepubertal males following unintentional secondary exposure to estradiol spray/gel have been reported. In most cases, the condition resolved with removal of estradiol exposure. Divigel contains propylene glycol and therefore may cause skin irritation.

Interaction: The metabolism of oestrogens may be increased by drugs or herbal products that induce certain enzymes, such as CYP3A4. Hormone contraceptives and HRT, containing oestrogens have been shown to significantly decrease plasma concentrations of lamotrigine when co-administered, which may reduce seizure control.

Undesirable Effects: during the first few months of treatment, breakthrough bleeding, spotting and breast tenderness or enlargement can occur. These are usually temporary and normally disappear after continued treatment. Common adverse drug reactions (ADRs): weight increase, weight decrease, depression, nervousness, lethargy, headache, dizziness, hot flushes, nausea, vomiting, stomach cramps, flatulence, abdominal pain, rash, pruritus, unscheduled vaginal bleeding or spotting, vaginal discharge, disorder of vulva/vagina, menstrual disorder, breast tension/pain, skin irritation, application site pain, increased sweating, oedema. Uncommon ADRs: benign breast neoplasm, benign endometrial neoplasm, hypersensitivity reaction, increased appetite, hypercholesterolemia, anxiety, insomnia, apathy, emotional lability, impaired concentration, changes in libido and mood, euphoria, agitation, migraine, paraesthesia, tremor, visual impairment, dry eye, palpitations, hypertension, superficial phlebitis, purpura, dyspnoea, rhinitis, constipation, dyspepsia, diarrhoea, rectal disorder, acne, alopecia, dry skin, nail disorder, skin nodule, hirsutism, erythema nodosum, urticarial, joint disorders, muscle cramps, increased urinary frequency/urgency, urinary incontinence, cystitis, urine discoloration, haematuria, breast enlargement, breast tenderness, endometrial hyperplasia, uterine disorder, fatigue, abnormal laboratory test, asthenia, fever, flu syndrome, malaise. Rare ADRs: contact lens intolerance, venous thromboembolism, alterations in liver function and biliary flow, dysmenorrhea, pre-menstrual like syndrome. ADRs with unknown frequency: uterine fibroids, exacerbation of hereditary angioedema, cerebral ischaemic events, bloating, cholestatic jaundice, contact dermatitis, eczema. Other adverse reactions have been reported in association with oestrogen-progestagen treatment: oestrogen-dependent neoplasms benign and malignant, myocardial infarction and stroke, gall bladder disease, skin and subcutaneous disorders (chloasma, erythema multiforme vascular purpura), probable dementia over the age of 65. Prescribers should consult the SmPC in relation to other side effects. **Legal Category:** POM S1A. **Product Authorisation Number:** Divigel PA 1327/2/1. **Distributed by:** Orion Pharma (Ireland) Ltd. c/o Allphar Services Ltd, 4045 Kingswood Road, Citywest Business Park, Co Dublin, Ireland . Full prescribing information is available on request. **Divigel** is a registered trademark.

Date of Revision of the text: February 2024.

Adverse effects should be reported. You can report side effects directly via the Health Products Regulatory Authority (HPRA) website: www.hpra.ie or by email on medsafety@hpra.ie. Adverse effects should also be reported to Orion Pharma via ie.medicalinformation@orionpharma.com