SANDRENA

(Estradiol hemihydrate)

Prescribing Information: Sandrena (estradiol hemihydrate)

Sandrena 0.5 mg and 1mg gel (estradiol hemihydrate)

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

Dosage and Administration: For transdermal use. Sandrena 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. The lowest effective dose for the shortest duration should be used. In patients with an intact uterus, combine Sandrena 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 once daily on dry & clean skin of the lower trunk or the right or left thigh on alternate days. Application surface should be 1-2 times the size of a hand. Do not apply on breasts, face, eyes or irritated skin. After application: allow gel to dry for a few minutes and do not wash within 1 hour, wash hands with soap and water. If another person touches the site, that area should be washed with soap and water.

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, known thrombophilic disorders, active or recent arterial thromboembolic disease, acute liver disease or a history of liver disease as long as liver functions have failed to return to normal, hypersensitivity to the active substance or to any of the excipients, porphyria. **Warnings and Precautions:** For treatment of postmenopausal symptoms, HRT should only be initiated for symptoms that adversely affect quality of life. Carefully appraise the risks and benefits at least annually and only continue as long as the benefit outweighs the risk. Evidence of the risks in the treatment of premature menopause is limited. Due to the low level of absolute risk in younger women the balance of benefits and risks for these women may be more favourable than in older women. Before initiating or reinstituting HRT take a complete personal & family medical history. Physical examination should be guided by this and by the contraindications & warnings for use. Periodic check-ups during treatment recommended. 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:* present or previous conditions, and/or those aggravated by pregnancy or previous hormone treatment may recur or be aggravated during treatment with Sandrena, in particular: leiomyoma or endometriosis, risk factors for thromboembolic disorders or oestrogen dependent tumours, hypertension, liver disorders, diabetes mellitus with or without vascular involvement, cholelithiasis, migraine or severe headache, systemic lupus erythematosus, history of endometrial hyperplasia, epilepsy, asthma, otosclerosis, angioedema. *Reasons for immediate withdrawal of therapy:* if a contra-indication is discovered, jaundice or deterioration in liver function, significant increase in blood pressure, new onset of migraine-type headache, pregnancy. In women with an intact uterus the risk of endometrial hyperplasia and carcinoma is increased when oestrogens are administered alone for prolonged periods. 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 & spotting may occur during the first months of treatment. Investigate if breakthrough bleeding or spotting appears after some time on therapy, or continues after treatment stopped. 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. Evidence suggests an increased risk of breast cancer in women taking combined oestrogen-progestagen and possibly also oestrogen-only HRT, that is dependent on the duration of taking HRT. After stopping treatment, the excess risk decreases with time & 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:* 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 & diminishes over time after stopping. *Venous thromboembolism (VTE):* HRT is associated with a 1.3–3 fold risk of VTE, it is more likely in the first year of HRT than later. 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 in these patients. Prophylactic measures need to be considered to prevent VTE following surgery. If prolonged immobilisation is to follow elective surgery, temporarily stopping HRT 4 to 6 weeks earlier is recommended. Treatment should not be restarted until the woman is completely mobilized. Carefully consider risk-benefits of HRT use in women already on chronic anticoagulant treatment. If VTE develops after initiating therapy, discontinued & advise patients to contact their doctors immediately when they are aware of a potential thromboembolic symptom. *Coronary artery disease (CAD):* There is no evidence of protection against myocardial infarction in women with or without existing CAD who received combined oestrogen-progestagen or oestrogen-only HRT. The relative risk of CAD during use of combined oestrogen+progestagen HRT is slightly increased. As the baseline absolute risk of CAD is strongly dependent on age, the number of extra cases of CAD due to oestrogen+progestagen use is very low in healthy women close to menopause, but will rise with more advanced age. Combined oestrogen-progestagen and oestrogen-only therapy are associated with an up to 1.5-fold increase in risk of ischaemic stroke. Closely observe patients with cardiac or renal dysfunction, terminal renal insufficiency, pre-existing hypertriglyceridemia. Exogenous oestrogens may induce or exacerbate symptoms of hereditary and acquired angioedema. Oestrogens increase thyroid binding globulin (TBG), leading to increased circulating total thyroid hormone. T3 resin uptake is decreased, reflecting elevated TBG. Other binding proteins may be elevated (CBG, SHBG). 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. Women with a tendency to chloasma should minimize exposure to the sun or ultraviolet radiation whilst taking HRT. 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. Due to the limited data, caution is warranted for co-administration with ombitasvir/paritaprevir/ritonavir with or without dasabuvir, & the regimen glecaprevir/pibrentasvir. Patients should not allow others, especially children, to come into contact with the exposed area of the skin. Product contains propylene glycol & alcohol so may cause a burning sensation on damaged skin. **Interactions:** The metabolism of oestrogens may be increased by drugs that induce CYP450 enzymes (specific anti-convulsants & anti-infectives, herbal products containing St. John's wort). Ritonavir & nelfinavir have inducing properties when used with steroid hormones. Many combinations of HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors including combinations with HCV inhibitors can increase or decrease plasma concentrations of oestrogen. Net effect of these changes may be clinically relevant in some cases. Prescribing information of concomitant medications should be consulted to identify potential interactions and recommendations. Transdermally applied oestrogens might be less affected than oral hormones by enzyme inducers. Increased metabolism of oestrogens and progestogens may lead to decreased effect and changes in uterine bleeding profile. Hormone contraceptives containing oestrogens have been shown to significantly decrease plasma concentrations of lamotrigine when co-administered, which may reduce seizure control. **Pregnancy & Lactation:** Sandrena is not indicated during pregnancy. If pregnancy occurs during medication with Sandrena, treatment should be withdrawn immediately. Sandrena is not indicated during lactation. **Undesirable Effects:** During the first few months of treatment breakthrough bleeding, spotting and breast tenderness or enlargement can occur (usually temporary and normally disappear after continued treatment). *Common:* 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 pain/tension, skin irritation, application site, pain, increased sweating, edema. *Uncommon:* 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, urticaria, 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:* Contact lens intolerance, venous thromboembolism, alterations in liver function and biliary flow, dysmenorrhea, pre-menstrual like syndrome. *Frequency not known:* Uterine fibroids, exacerbation of angioedema, cerebral ischaemic events, bloating (abdominal distension), cholestatic jaundice, contact dermatitis, eczema. *Other:* 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. **Marketing Authorisation Numbers:** Sandrena 0.5mg Gel: 28 sachets, £5.08 PL 27925/0015. Sandrena 1mg Gel: 28 sachets, £5.85, 91 sachets £17.57 PL 27925/0016. **Marketing Authorisation Holder:** Orion Corporation, Orionintie 1, FI-02200 Espoo, Finland. Distributed by Orion Pharma (UK) Ltd, Abbey Gardens, 4 Abbey Street, Reading, RG1 3BA, UK.Sandrena is a registered trademark.

Date of Prescribing Information: April 2024

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard.

Adverse events should also be reported to Orion Pharma (UK) Ltd on 01635 520300.