INDIVINA

(Estradiol valerate/ Medroxyprogesterone acetate)

Prescribing Information : Indivina (Estradiol valerate/Medroxyprogesterone acetate)

Indivina 1 mg/2.5 mg tablets, Indivina 1 mg/5 mg tablets, Indivina 2 mg/5 mg tablets (Estradiol valerate/Medroxyprogesterone acetate)

Indication: Hormone replacement therapy (HRT) for oestrogen deficiency symptoms in women with an intact uterus more than three years after menopause. Prevention of osteoporosis in postmenopausal women at high risk of future fractures who are intolerant of, or contraindicated for, other medicinal products approved for the prevention of osteoporosis. Experience of treating women older than 65 years is limited.

Dosage and Administration: For oral use. One tablet each day without a tablet-free interval. Treatment is recommended to be initiated with Indivina 1 mg/2.5 mg tablet. Depending on the clinical response to treatment, the dosage can then be adjusted to individual needs. Medroxyprogesterone acetate (MPA) 2.5 mg is usually sufficient to prevent breakthrough bleeding. If breakthrough bleeding occurs and persists, and endometrial abnormality has been ruled out, the dose can be increased to 5 mg (Indivina 1mg/5 mg tablet). If 1 mg of estradiol valerate (E2V) is not sufficient to alleviate oestrogen deficiency symptoms, the dose can be increased to 2 mg (Indivina 2 mg/5 mg tablet). **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, patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Warnings and Precautions: 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. *Medical examination/follow-up:* Before initiating or reinstituting HRT take a complete personal and family medical history. Physical examination should be guided by this and by the contraindications and 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, e.g. mammography, should be carried out in accordance with currently accepted screening practices, modified to the clinical needs of the individual. *Conditions which need supervision:* present conditions or those aggravated by pregnancy or previous hormone treatment may recur or be aggravated during treatment with Indivina, 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. *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. 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. Risk may remain elevated for at least 10 years after stopping therapy. 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. Break-through bleeding and spotting may occur during the first months of treatment. Investigate if break-through bleeding or spotting appears after some time on therapy, or continues after treatment stopped. *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. For combined oestrogen-progestagen therapy, the excess risk becomes apparent after approx. 3 years of use. For oestrogen only therapy, observational studies have mostly reported a small increase in risk of having breast cancer diagnosed that is lower than that found in users of oestrogen-progestagen combinations. After stopping treatment, the excess risk decreases 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:* 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. *Venous thromboembolism (VTE):* HRT is associated with a 1.3–3 fold risk of VTE. 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. General 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. 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 mobilised. Screen women with a first degree relative with a history of thrombosis at young age. Carefully consider risk-benefits of HRT use in women already on chronic anticoagulant treatment. If VTE develops after initiating therapy, discontinued and 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. 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. *Other conditions:* Closely observe patients with cardiac, renal dysfunction or 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. 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. *ALT Elevations:* During clinical trials with patients treated for hepatitis C with the combination regimen ombitasvir/paritaprevir/ritonavir with and without dasabuvir, ALT elevations greater than 5 times the upper limit of normal were significantly more frequent in women using ethinylestradiol-containing medicinal products such as CHCs. ALT elevations also observed in patients treated with glecaprevir/ pibrentasvir when using ethinylestradiol-containing medications. Due to the limited data, caution is warranted for co-administration with ombitasvir/ paritaprevir/ritonavir with or without dasabuvir, and the regimen glecaprevir/pibrentasvir.
Interaction: The metabolism of oestrogens and progestagens 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: The most frequently reported undesirable effect during Indivina treatment in clinical trials was breast tenderness, which occurred in 10.6% of users. *Common:* oedema, weight increase, weight decrease, depression, nervousness, lethargy, headache, dizziness, hot flushes, nausea, vomiting, stomach cramps, flatulence, breast pain/tension, unscheduled vaginal bleeding or spotting, vaginal discharge, disorder of vulva/vagina, menstrual disorder, increased sweating. *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, rash, dysmenorrhea, pre-menstrual like syndrome. *Frequency not known:* Uterine fibroids, exacerbation of angioedema, cerebral ischaemic events, abdominal pain, bloating, cholestatic jaundice, eczema. **Other:** Oestrogen-dependent neoplasms benign and malignant, venous thromboembolism, myocardial infarction and stroke, gall bladder disease, skin and subcutaneous disorders: chloasma, erythema multiforme, probable dementia over the age of 65, pancreatitis. Prescribers should consult the SmPC in relation to other side effects. **Legal Category:** POM. **Marketing Authorisation Numbers:** Indivina 1 mg/2.5 mg tablets: 3x28 tablets, £20.58 PL 27925/0011. Indivina 1 mg/5 mg tablets: 3x28 tablets, £20.58 PL 27925/0012. Indivina 2 mg/5 mg tablets: 3x28 tablets, £20.58 PL 27925/0013. **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. Full prescribing information is available on request. Indivina is a registered trademark. **Date of Prescribing Information:** February 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.