Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Indivina 1 mg/2.5 mg tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One Indivina 1 mg/2.5 mg tablet contains:
Estradiol valerate 1 mg
Medroxyprogesterone acetate 2.5 mg

Excipient with known effect
78.9 mg lactose (as monohydrate).
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.
White, round, bevelled-edge, diameter 7 mm, flat tablets with a code on one side with 1+2.5

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hormone replacement therapy (HRT) for estrogen 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. (See also sections 4.4 and 5.1)
The experience of treating women older than 65 years is limited.

4.2 Posology and method of administration

Indivina is a continuous combined HRT regimen in which estrogen and progestagen are given every day without interruption.

Posology

One tablet each day orally without a tablet-free interval. Tablet should be taken approximately at the same time of the day. 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 (E_2V) is not sufficient to alleviate oestrogen deficiency symptoms, the dose can be increased to 2 mg (Indivina 2 mg/5 mg tablet).

In women with amenorrhea and not taking HRT or women who switch from another continuous combined HRT product, treatment with Indivina may be started on any day. Women who switch from cyclic HRT regimen should start Indivina treatment one week after completion of the cycle.

The effect of oestrogen on bone mineral density is dose dependent and therefore the effect of 1 mg E_2V may be less than with 2 mg (see section 5.1).

If the patient has forgotten to take one tablet, the forgotten tablet is to be discarded. Forgetting a dose may increase the likelihood of breakthrough bleeding and spotting.

For initiation and continuation of treatment of postmenopausal symptoms, the lowest effective dose for the shortest duration (see also Section 4.4) should be used.

4.3 Contraindications

- Known, past or suspected breast cancer
- Known or suspected oestrogen-dependent malignant tumours (e.g. endometrial cancer)
- 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, see section 4.4)
- 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
- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1
- Porphyria

4.4 Special warnings and precautions for use

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 women, however, 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, 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 afrequency and nature adapted to the individual woman. Women should be advised what changes in their breasts should be reported to their doctor or nurse (see 'Breast cancer' below). 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

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 beaggravated during treatment with Indivina, in particular:
- Leiomyoma (uterine fibroids) or endometriosis
- Risk factors for thromboembolic disorders (see below)
- Risk factors for oestrogen dependent tumours, e.g. 1st degree heredity for breast cancer
- Hypertension
- Liver disorders (e.g. liver adenoma)
- Diabetes mellitus with or without vascular involvement
- Cholelithiasis
- Migraine or (severe) headache
- Systemic lupus erythematosus
- A history of endometrial hyperplasia (see below)
- Epilepsy
- Asthma
- Otosclerosis
- Angioedema (hereditary/acquired)

Reasons for immediate withdrawal of therapy

Therapy should be discontinued in case a contra-indication 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 (see section 4.8). 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, which may include endometrial biopsy to exclude endometrial malignancy.

Breast cancer

The overall evidence shows 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 randomised placebo-controlled trial 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 (1-4) years (see section 4.8).

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 lower than that found in users of oestrogen-progestagen combinations (see section 4.8).

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 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 WHI trial, suggest that use of combined HRTs may be associated with a similar or slightly smaller risk (see section 4.8).

Venous thromboembolism

- HRT is associated with a 1.3-3 fold risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of HRT than later (see section 4.8).

- 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 (see section 4.3).

- Generally recognised risk factors for VTE include, use of oestrogens, older age, major surgery, prolonged immobilisation, obesity (BMI > 30 kg/m^2), pregnancy/postpartum period, systemic lupus erythematosus (SLE), and cancer. There is no consensus about the possible role of varicose veins in VTE.

- As in all postoperative 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 mobilised.

- In women with no personal history of VTE but with a first degree relative with a history of thrombosis at young age, screening may be offered after careful counselling regarding its limitations (only a proportion of thrombophilic defects are identified by screening).

If a thrombophilic defect is identified which segregates with thrombosis in family members or if the defect is 'severe' (e.g. antithrombin, protein S, or protein C deficiencies or a combination of defects) 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 (e.g. painful swelling of a leg, sudden pain in the chest, dyspnoea).

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. 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.

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 therapies 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 (see section 4.8).

Other conditions

- Oestrogens may cause fluid retention and, therefore, patients with cardiac or renal dysfunction should be carefully observed.
- Women with pre-existing hypertriglyceridaemia should be followed closely during oestrogen replacement or hormone replacement therapy, since rare cases of large increases of plasma triglycerides leading to pancreatitis have been reported with oestrogen therapy in this condition.
- 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, as measured by protein-bound iodine (PBI), T4 levels (by column or by radio-immunoassay) or T3 levels (by radio-immunoassay). T3 resin uptake is decreased, reflecting the elevated TBG. Free T4 and free T3 concentrations are unaltered. Other binding proteins may be elevated in serum, i.e. corticoid binding globulin (CBG), sex-hormone-binding globulin (SHBG) leading to 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.Women with a tendency to chloasma should minimise 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 virus (HCV) infections with the combination regimen ombitasvir/paritaprevir/ritonavir with and without dasabuvir, ALT elevations greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinylestradiol-containing medicinal products such as CHCs. Additionally, also in patients treated with glecaprevir/pibrentasvir, ALT elevations were observed in women using ethinylestradiol-containing medications such as CHCs. Women using medicinal products containing oestrogens other than ethinylestradiol, such as estradiol, had a rate of ALT elevation similar to those not receiving any oestrogens; however, due to the limited number of women taking these other oestrogens, caution is warranted for co-administration with the combination drug regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir and also the regimen glecaprevir/pibrentasvir. See section 4.5.

Excipients

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

The metabolism of oestrogens and progestagens may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically cytochrome P450 enzymes, such as anticonvulsants (e.g. phenobarbital, phenytoin, carbamazepine) and anti-infectives (e.g. rifampicin, rifabutin, nevirapine, efavirenz).

Ritonavir and nelfinavir, although known as strong inhibitors, by contrast exhibit inducing properties when used concomitantly with steroid hormones. When co-administered with sex 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. The net effect of these changes may be clinically relevant in some cases.

Therefore, the prescribing information of concomitant medications including HIV/HCV antivirals should be consulted to identify potential interactions and any related recommendations.

Herbal preparations containing St John's wort (*Hypericum perforatum*) may induce the metabolism of oestrogens and progestagens.

Clinically, an increased metabolism of oestrogens and progestagens may lead to decreased effect and changes in the uterine bleeding profile.

Effect of HRT with oestrogens on other medicinal products

Hormone contraceptives containing oestrogens have been shown to significantly decrease plasma concentrations of lamotrigine when co-administered due to induction of lamotrigine glucuronidation. This may reduce seizure control. Although the potential interaction between hormone replacement therapy and lamotrigine has not been studied, it is expected that a similar interaction exists, which may lead to a reduction in seizure control among women taking both medicinal products together.

Pharmacodynamic interactions

During clinical trials with the HCV combination drug regimen ombitasvir/paritaprevir/ritonavir with and without dasabuvir, ALT elevations greater than 5 times the upper limit of normal (ULN) were significantly more frequent in women using ethinylestradiol-containing medicinal products such as CHCs. Women using medicinal products containing oestrogens other than ethinylestradiol, such as estradiol, had a rate of ALT elevation similar to those not receiving any oestrogens; however, due to the limited number of women taking these other oestrogens, caution is warranted for co-administration with the combination drug regimen ombitasvir/paritaprevir/ritonavir with or without dasabuvir and also the regimen with glecaprevir/pibrentasvir (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

Indivina is not indicated during pregnancy. If pregnancy occurs during medication with Indivina, treatment should be withdrawn immediately. Data on limited number of exposed pregnancies indicate no adverse effects of medroxyprogesterone acetate on the foetus. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

The results of most epidemiological studies to date relevant to inadvertent foetal exposure to combinations of estrogens and progestagen indicate no teratogenic or foetotoxic effect.

Breastfeeding

Indivina is not indicated during lactation.

4.7 Effects on ability to drive and use machines

Indivina has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The most frequently reported undesirable effect during Indivina treatment in clinical trials was breast tenderness, which occurred in 10.6% of users.

Undesirable effects according to system organ class associated with HRTtreatment are presented in the table below.

Organ system class	**Common ADRs, ≥1/100 <10**	**Uncommon ADRs, ≥1/1000 <1/100**	**Rare ADRs, ≥1/10 000 <1/1 000**	**Adverse events reported post marketing with frequency not known (cannot be estimated**

				from the available data)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		Benign breast neoplasm, benign endometrial neoplasm		Uterine fibroids
Immune system disorders		Hypersensitivity reaction		Exacerbation of angioedema (hereditary and acquired)
Metabolism and nutrition disorders	Oedema, weight increase, weight decrease	Increased appetite, hypercholesterolemia[1]		
Psychiatric disorders	Depression, nervousness, lethargy	Anxiety, insomnia, apathy, emotional lability, impaired concentration, changes in mood or libido, euphoria[1], agitation[1]		
Nervous system disorders	Headache, dizziness	Migraine, paraesthesia, tremor[1]		
Eye disorders		Visual impairment, dry eye[1]	Contact lense intolerance	
Cardiac disorders		Palpitations		
Vascular disorders	Hot flushes	Hypertension[1], superficial phlebitis[1], purpura[1]	Venous thromboembolism (i.e. deep leg or pelvic venous thrombosis and pulmonary embolism)[2]	Cerebral ischaemic events
Respiratory, thoracic and mediastinal disorders		Dyspnoea[1], rhinitis[1]		
Gastrointestinal disorders	Nausea, vomiting, stomach cramps, flatulence	Constipation, dyspepsia[1], diarrhoea[1], rectal disorder[1]		Abdominal pain, bloating (abdominal distension)
Hepatobiliary disorders			Alterations in liver function and biliary flow	Cholestatic jaundice
Skin and subcutaneous tissue disorders		Acne, alopecia, dry skin, nail disorder[1], skin nodule[1], hirsuitism[1], erythema nodosum, urticaria	Rash	Eczema
Musculoskeletal and connective tissue disorders		Joint disorders, muscle cramps		
Renal and urinary disorders		Increased urinary frequency/urgency, urinary incontinence[1], cystitis[1], urine discoloration[1], haematuria[1]		
Reproductive system and	Breast pain/tension,	Breast enlargement, breast tenderness, endometrial hyperplasia, uterine disorder[1]	Dysmenorrhea, pre-menstrual like	

breast disorders	unscheduled vaginal bleeding or spotting, vaginal discharge, disorder of vulva/vagina, menstrual disorder		syndrome	
General disorders and administration site conditions	Increased sweating	Fatigue, abnormal laboratory test[1], asthenia[1], fever[1], flu syndrome[1], malaise[1]		

1. have been reported in single cases in clinical trials. Given the small study population (n=611) it cannot be determined based on these results if the events are uncommon or rare.
2. see section 4.3 and 4.4

Other adverse reactions have been reported in association with oestrogen/progestagen treatment:

Myocardial infarction
Gall bladder disease

Skin and subcutaneous disorders: chloasma, erythema multiforme

Probable dementia over the age of 65 (see section 4.4)

Pancreatitis (see section 4.4)

Breast cancer risk

- An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking combined oestrogen-progestagen therapy for more than 5 years.
- The increased risk in users of oestrogen-only therapy is lower than that seen in users of oestrogen-progestagen combinations.
- The level of risk is dependent on the duration of use (see section 4.4).
- Absolute risk estimations based on results of the largest randomised placebo-controlled trial (WHI-study) and the largest meta-analysis of prospective epidemiological studies are presented. **Largest meta-analysis of prospective epidemiological studiesEstimated additional risk of breast cancer after 5 years' use in women with BMI 27 (kg/m^2)**

Age at start HRT (years)	Incidence per 1000 never-users of HRT over a 5 year period (50-54 years)*	Risk ratio	Additional cases per 1000 HRT users after 5 years
Oestrogen only HRT			
50	13.3	1.2	2.7
Combined oestrogen-progestagen			
50	13.3	1.6	8.0

*Taken from baseline incidence rates in England in 2015 in women with BMI 27 (kg/m2)
Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately.

Estimated additional risk of breast cancer after 10 years' use in women with BMI 27 (kg/m^2)

Age at start HRT (years)	Incidence per 1000 never-users of HRT over a 10 year period (50-59 years) *	Risk ratio	Additional cases per 1000 HRT users after 10 years
Oestrogen only HRT			
50	26.6	1.3	7.1
Combined oestrogen-progestagen			
50	26.6	1.8	20.8

* Taken from baseline incidence rates in England in 2015 in women with BMI 27 (kg/m^2)
Note: Since the background incidence of breast cancer differs by EU country, the number of additional cases of breast cancer will also change proportionately.

US WHI studies - additional risk of breast cancer after 5 years' use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio & 95%CI	Additional cases per 1000 HRT users over 5 years (95%CI)
CEE oestrogen-only			
50-79	21	0.8 (0.7 – 1.0)	-4 (-6 – 0)*
CEE+MPA oestrogen & progestagen‡			
50-79	17	1.2 (1.0 – 1.5)	+4 (0 – 9)

** WHI study in women with no uterus, which did not show an increase in risk of breast cancer*

‡When the analysis was restricted to women who had not used HRT prior to the study there was no increased risk apparent during the first 5 years of treatment: after 5 years the risk was higher than in non-users.

Endometrial cancer risk

Postmenopausal women with a uterus
The endometrial cancer risk is about 5 in every 1000 women with a uterus not using HRT. In women with a uterus, use of oestrogen-only HRT is not recommended because it increases the risk of endometrial cancer (see section 4.4).

Depending on the duration of oestrogen-only use and oestrogen dose, the increase in risk of endometrial cancer in epidemiology studies varied from between 5 and 55 extra cases diagnosed in every 1000 women between the ages of 50 and 65.

Adding a progestagen to oestrogen-only therapy for at least 12 days per cycle can prevent this increased risk. In the Million Women Study the use of five years of combined (sequential or continuous) HRT did not increase risk of endometrial cancer (RR of 1.0 (0.8-1.2)).

Ovarian cancer risk

Use of oestrogen-only or combined oestrogen-progestagen HRT has been associated with a slightly increased risk of having ovarian cancer diagnosed (see section 4.4). 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.

Risk of venous thromboembolism

HRT is associated with a 1.3-3-fold increased relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of using HRT (see section 4.4). Results of the WHI studies are presented:

WHI Studies - Additional risk of VTE over 5 years' use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio and 95%CI	Additional cases per 1000 HRT users
Oral oestrogen-only*			
50-59	7	1.2 (0.6-2.4)	1 (-3 – 10)
Oral combined oestrogen-progestagen			

50-59	4	2.3 (1.2 – 4.3)	5 (1 - 13)

**Study in women with no uterus*

Risk of coronary artery disease

- The risk of coronary artery disease is slightly increased in users of combined oestrogen-progestagen HRT over the age of 60 (see section 4.4).

Risk of ischaemic stroke

- The use of oestrogen-only and oestrogen + progestagen therapy is associated with an up to 1.5 fold increased relative risk of ischaemic stroke. The risk of haemorrhagic stroke is not increased during use of HRT.

- This relative risk is not dependent on age or on duration of use, but as the baseline risk is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age, see section 4.4.

WHI studies combined - Additional risk of ischaemic stroke* over 5 years' use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio and 95%CI	Additional cases per 1000 HRT users over 5 years
50-59	8	1.3 (1.1 1.6)	3 (1-5)

**no differentiation was made between ischaemic and haemorrhagic stroke.*

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system:
HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

Oestrogen overdose may cause nausea, headache and uterine bleeding. Numerous reports on high doses of oestrogen-containing oral contraceptives ingested by young children indicate that serious harmful effects do not occur. Treatment of oestrogen overdose is symptomatic. High doses of medroxyprogesterone acetate (MPA) used for cancer treatment have not resulted in serious undesirable effects.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Progestagens and oestrogens, fixed combinations;
ATC code: G03FA12.
The active ingredient, synthetic 17β-estradiol, is chemically and biologically identical to endogenous human estradiol. It substitutes for the loss of oestrogen production in menopausal women, and alleviates menopausal symptoms.

Oestrogens prevent bone loss following menopause or ovariectomy.

Medroxyprogesterone acetate is a derivative of the natural progesterone, 17-alpha-hydroxy-6-methylprogesterone. Medroxyprogesterone acetate binds to progestin-specific receptors and acts on the endometrium to convert the status of the endometrium from proliferative to secretory.

As oestrogens promote the growth of the endometrium, unopposed oestrogens increase the risk of endometrial hyperplasia and cancer. The addition of medroxyprogesterone acetate greatly reduces the oestrogen-induced risk of endometrial hyperplasia in non-hysterectomised women.

Clinical trial information

Relief of oestrogen deficiency symptoms and bleeding patterns

- Relief of menopausal symptoms was achieved during the first few weeks of treatment.

- Amenorrhoea was seen in 91% of women receiving 1 mg estradiol valerate and in 80% of women receiving 2 mg estradiol valerate after 10-12 months of treatment. Irregular bleeding and/or spotting appeared in 41% of the women receiving 1 mg estradiol valerate and 51% of women receiving 2 mg estradiol valerate during the first three months of treatment and in 9% of the women receiving 1 mg estradiol valerate and in 20% of women receiving 2 mg estradiol valerate during 10-12 months of treatment.

Prevention of osteoporosis
- Oestrogen deficiency at menopause is associated with an increasing bone turnover and decline in bone mass. The effect of oestrogens on bone mineral density (BMD) is dose dependent. Protection appears to be effective for as long as treatment is continued. After discontinuation of HRT, bone mass is lost at a rate similar to that in untreated women.

- Evidence from the WHI trial and meta-analysed trials shows that current use of HRT, alone or in combination with a progestagen – given to predominantly healthy women – reduces the risk of hip, vertebral, and other osteoporotic fractures. HRT may also prevent fractures in women with low bone density and/or established osteoporosis, but the evidence for that is limited.

- After 4 years of treatment with Indivina combinations containing the 1 mg dose, the increase in lumbar spine bone mineral density (BMD) was 6.2 ± 0.5% (mean ± SD). The percentage of women who maintained or gained BMD in lumbar zone during treatment was 86.6 %.

- Indivina combinations containing the 1 mg dose also had an effect on hip BMD. The increase after 4 years was 2.9 ± 0.4% (mean ± SD) at femoral neck. The percentage of women who gained BMD in hip zone during treatment was 80.4 %.

- After 4 years of treatment with Indivina combinations containing the 2 mg dose, the increase in lumbar spine BMD was 7.4 ± 0.4% (mean ± SD). The percentage of women who gained BMD in lumbar zone during treatment was 95.8 %.

- Indivina combinations containing the 2 mg dose also had an effect on hip BMD. The increase after 4 years was 2.9 ± 0.4% (mean ± SD) at femoral neck. The percentage of women who gained BMD in hip zone during treatment was 72.3 %.

5.2 Pharmacokinetic properties

Following oral administration estradiol valerate is absorbed from the gastrointestinal tract and rapidly hydrolysed to estradiol by esterases. In postmenopausal women aged 50-65 years themaximum concentration of estradiol in serum (C_{max}) was reached within 4 to 6 hours after multiple dosing of 1 mg or 2 mg estradiol valerate. After 1 mg dose C_{max} was about 166 pmol/l, trough concentration (C_{min}) about 101 pmol/l and average concentration ($C_{average}$) about 123 pmol/l. For 2 mg dose C_{max} was 308 pmol/l, C_{min} 171 pmol/l and $C_{average}$ 228 pmol/l. Comparable estradiol concentrations were observed in women over 65 years. Circulating estradiol is bound to plasma proteins, mainly to sex hormone binding globulin (SHBG) and serum albumin. Estradiol undergoes extensive biotransformation. Its metabolites are excreted in the urine as glucuronide and sulfate conjugates together with a small proportion of unchanged estradiol. Besides urinary excretion, oestrogen metabolites undergo an enterohepatic circulation. Only a small amount of a dose is excreted in the faeces.
The absorption of medroxyprogesterone acetate after oral administration is low due to low solubility and there is large individual variation. Medroxyprogesterone acetate undergoes virtually no first-pass metabolism. After multiple dosing of 2.5 mg or 5 mg medroxyprogesterone acetate to women aged 50-65 years, maximum concentration in serum was reached in less than 2 hours. After 2.5 mg dose C_{max} was about 0.37 ng/ml, C_{min} about 0.05 ng/ml and $C_{average}$ about 0.11 ng/ml. After 5 mg dose C_{max} was about 0.64 ng/ml, C_{min} about 0.12 ng/ml and $C_{average}$ about 0.21 ng/ml. Comparable medroxyprogesterone acetate concentrations were observed in women over 65 years.
Medroxyprogesterone acetate is over 90% bound to plasma proteins, mainly to albumin. The elimination half-life of oral medroxyprogesterone acetate is approximately 24 hours. Medroxyprogesterone acetate is extensively metabolised by hepatic hydroxylation and conjugation and excreted in the urine and the bile. Metabolism is poorly documented and the pharmacological activity of the metabolites is not known.

5.3 Preclinical safety data

Animal studies with estradiol and medroxyprogesterone acetate have shown expected estrogenic and gestagenic effects. Both compounds induced adverse effects in reproductive toxicity studies. Chiefly, estradiol showed embryotoxic effects and induced feminisation of male foetuses.
Medroxyprogesterone showed embryotoxic effects and induced anti-androgenic effects in male foetuses and masculinization in female foetuses. The relevance of these data for human exposure is unknown (see section 4.6). Concerning other preclinical effects, the toxicity profiles of estradiol valerate and medroxyprogesterone acetate are well known and reveal no particular

human health risks beyond those discussed in other sections of the SPC and which generally apply to hormone replacement therapy.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Maize starch
Gelatin
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 25 °C. Store in the original package in order to protect from moisture.

6.5 Nature and contents of container

28 tablets in PVC/PVDC/Aluminium blister. Pack of 1x 28 tablets and 3x 28 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Anyunused medicinal product or waste material should be disposed of in accordancewith local requirements.

7 MARKETING AUTHORISATION HOLDER

Orion Corporation
Orionintie 1
FI-02200 Espoo
Finland

8 MARKETING AUTHORISATION NUMBER

PA1327/005/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 21July 2000
Date of last renewal: 10December 2009

10 DATE OF REVISION OF THE TEXT

November 2023