SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Elleste Solo MX 40 micrograms Transdermal Patch

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Elleste Solo MX 40 contains 1.25 mg of estradiol (as hemihydrate) with a surface area of active surface area of 14.25 cm^2 and each patch delivers approximately 40 micrograms of estradiol per 24 hours.

For the full list of excipients, see 6.1.

3 PHARMACEUTICAL FORM

Transdermal patch.

Elleste Solo MX 40 is a self-adhesive, flexible transdermal patch comprising a layer of clear adhesive sandwiched between a translucent patch and a metallised polyester backing. Elleste Solo MX 40 is a rectangular shape with rounded corners.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hormone replacement therapy (HRT) for estrogen deficiency symptoms in peri-menopausal and post-menopausal women.

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 Section 4.4).

The experience of treating women older than 65 years is limited.

4.2 Posology and method of administration

Posology

Elleste Solo MX 40 Transdermal Patch is an oestrogen-only patch applied to the skin twice weekly in order to ensure a continuous supply of estradiol to the body; thus, each used system is removed every 3-4 days and replaced by a new one.

Adults

Climacteric Symptoms:

For initiation and continuation of treatment of peri- and postmenopausal symptoms, the lowest effective dose for the shortest duration (see also Section 4.4) should be used. Therapy should be initiated with Elleste Solo MX 40 in women who have menopausal symptoms. The dosage may be increased if required by using Elleste Solo MX 80.

The treatment is generally initiated with Elleste Solo MX 40, but the selection of the initial dose can be based on the severity of the patient's symptoms. Depending on the clinical response to treatment, the dosage can then be adjusted to individual needs: if the patient presents with undesirable effects (e.g. breast tenderness and/or vaginal bleeding, the dose is probably excessive

and should be reduced. If the dose selected does not alleviate the symptoms of oestrogen deficiency, it should be increased.

In women with a uterus, a progestogen approved for addition to oestrogen treatment must be additionally administered for at least 12 -14 days every month/28 day cycle to oppose the development of an oestrogen-stimulated hyperplasia of the endometrium.

Dosage Schedule:

Therapy may start at any time in women with established amenorrhoea or who are experiencing long intervals between spontaneous menses. In women who are menstruating, it is advised that therapy starts within five days of the start of bleeding. Patients changing from a cyclical or continuous sequential preparation should complete the cycle, and after a withdrawal bleed, may then change to Elleste Solo MX 40. Patients changing from a continuous combined preparation may start therapy at any time if amenorrhoea is established, or otherwise start within five days of the start of bleeding.

Elleste Solo MX 40 should be given continuously and, in women with an intact uterus, a progestogen is recommended and should be added for at least 12-14 days each cycle. The benefits of the lower risk of endometrial hyperplasia and endometrial cancer, due to adding progestogen, should be weighed against the increased risk of breast cancer, (see Sections 4.4 and 4.8). Unless there is a previous diagnosis of endometriosis, it is not recommended to add a progestogen in hysterectomised women.

Method of administration

Elleste Solo MX 40 transdermal patch should be applied twice weekly on a continuous basis. Each patch should be removed after 3 to 4 days and replaced with a new patch applied to a slightly different site.

Apply the Elleste Solo MX 40 Transdermal Patch to the skin of the hip, upper quadrant of the buttock, lumbar region, or abdomen and press firmly over the whole surface and along the edges to ensure good adhesion. The absorption capacity of the skin is the rate-determining factor in the release of estradiol from Elleste Solo MX 40 Transdermal Patch. The application on another (higher) skin region than on the mentioned preferred regions is not recommended, as this might have an influence on the release of estradiol.

The skin of the application site has to be clean, dry, not greasy and free of redness or irritation. Areas of the body that form lots of folds during movement as well as sites from which the patch could fall off due to movement or rubbing should be avoided.

Elleste Solo MX 40 Transdermal Patch should not be applied on or near the breasts.

It is possible to take a shower or a bath while wearing the patch.

In the unlikely event that a patch should fall off (excess sweating, abnormal rubbing of clothing), it is recommended to re-stick it onto dry skin. In the event that a patch does come off, it should be replaced with a new patch. The patch should then be changed again at the regular time to re-establish the patient's routine schedule. Similarly, if the patch is not changed on the scheduled day, it should be replaced as soon as possible and changed again on the next scheduled day. Forgetting to apply a new patch at the scheduled time may increase the likelihood of break-through bleeding and spotting.

Paediatric population:

There is no relevant indication for the use of Elleste Solo MX 40 Transdermal Patch in the paediatric population.

4.3 Contraindications

Known hypersensitivity to the active substances or to any of the excipients listed in Section 6.1;
Known, past or suspected breast cancer;
Known or suspected oestrogen-dependent malignant tumours, (e.g. endometrial cancer);
Undiagnosed genital bleeding;
Untreated endometrial hyperplasia;
Active thrombophlebitis;
Previous idiopathic or current venous thromboembolism (deep vein 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;
Dubin-Johnson and Rotor Syndromes (or monitor closely);
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 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 (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.

<u>Conditions which need supervision:</u>

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 with Elleste Solo MX 40, in particular:
- Risk factors for oestrogen dependent tumours, e.g. 1st degree heredity for breast cancer (see below);
- Diabetes mellitus with or without vascular involvement;
- Migraine or (severe) headache;
- Epilepsy;
- A history of, or risk of factors for, thromboembolic disorders (see below);
- Systemic lupus erythematosus, SLE;
- Liver disorders (e.g. liver adenoma);
- Leiomyoma (uterine fibroids) or endometriosis;
- Otosclerosis;
- Cholelithiasis;
- A history of endometrial hyperplasia (see below);
- Hypertension;
- Asthma.

<u>Reasons for immediate withdrawal of therapy:</u>

Therapy should be discontinued in case a contra-indication is discovered and in the following situations:
- hepatitis, jaundice. liver enlargement or deterioration in liver function;
- significant increase in blood pressure or blood pressure above systolic 160 mmHg or diastolic 95 mmHg;

- serious neurological effects including new onset of migraine-type headache, unusual severe, prolonged headache especially if first time or getting progressively worse *or* sudden partial or complete loss of vision *or* sudden disturbance of hearing or other perceptual disorders *or* dysphasia *or* bad fainting attack or collapse *or* first unexplained epileptic seizure *or* weakness, motor disturbances, very marked numbness suddenly affecting one side or one part of body;
- sudden severe chest pain (even if not radiating to left arm);
- sudden breathlessness (or cough with blood-stained sputum);
- unexplained swelling or severe pain in calf of one leg;
- severe stomach pain;
- prolonged immobility after surgery or leg injury;
- 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 progestogen cyclically for at least 12 days per month/28 day cycle or continuous combined oestrogen-progestogen therapy in non-hysterectomised women prevents the excess risk associated with oestrogen-only HRT.

The endometrial safety of added progestogen has not been demonstrated for oral doses of estradiol >2 mg and patches >50 µg/day.

The reduction in risk to the endometrium should be weighed against the increase in the risk of breast cancer of added progestogen (See 'Breast Cancer' below, and in Section 4.8).

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.

Unopposed oestrogen stimulation may lead to premalignant or malignant transformation in the residual foci of endometriosis. Therefore, the addition of progestogens to oestrogen replacement therapy should be considered in women who have undergone hysterectomy because of endometriosis, if they are known to have residual endometriosis, (but see above).

Breast Cancer

The overall evidence shows an increased risk of breast cancer in women taking combined oestrogen-progestogen or oestrogen-only HRT, that is dependent on the duration of taking HRT.

Combined oestrogen-progestogen 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-progestogen 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-progestogen 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-progestogen combined treatment, increases the density of mammographic images which may adversely affect the radiological detection of breast cancer.

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).

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 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.

Patients with 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).

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.

Those 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 doctor immediately when they are aware of a potential thromboembolic symptom (e.g. painful swelling of a leg, sudden pain in the chest, dyspnea).

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-progestogen or oestrogen-only HRT.

Combined oestrogen-progestogen therapy

The relative risk of CAD during use of combined oestrogen+progestogen 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+progestogen 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-progestogen 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 (see Section 4.8).

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-progestogen HRT, which becomes apparent within 5 years of use and diminishes over time after stopping.

Some other studies, including the WHI trial, suggest that the use of combined HRTs may be associated with a similar, or slightly smaller risk (see Section 4.8).

Other Conditions

Oestrogens may cause fluid retention and therefore patients with cardiac or renal dysfunction should be carefully observed. Patients with terminal renal insufficiency should be closely observed, since it is expected that the level of circulating active ingredients in Elleste Solo MX 40 is increased.

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 estrogens 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 biologically active hormone concentrations are unchanged. Other plasma proteins may be increased (angiotensinogen/renin substrate, alpha-1-antitrypsin, ceruloplasmin).

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.

In rare cases benign, and in even rarer cases malignant liver tumours leading in isolated cases to life-threatening intra-abdominal haemorrhage have been observed after the use of hormonal substances such as those contained in Elleste Solo MX 40. If severe upper abdominal complaints, enlarged liver or signs of intra-abdominal haemorrhage occur, a liver tumour should be considered in the differential diagnosis.

Women who may be at risk of pregnancy should be advised to adhere to non-hormonal contraceptive methods.

The requirement for oral anti-diabetics or insulin can change as a result of the effect on glucose tolerance.

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.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Oestrogens antagonise the effects of the phenindione.

The efficacy of oestrogens might be impaired:

- The metabolism of oestrogens may be increased by concomitant use of substances known to induce drug-metabolising enzymes, specifically cytochrome P450 enzymes 2B6, 3A4, 3A5, 3A7, such as anticonvulsants, (e.g. carbamazepine, phenobarbital, phenytoin) and anti-infectives, (e.g. rifampicin, rifabutin, nevirapine, or efavirenz).
- Ritonavir and nelfinavir, although known strong inhibitors CYP450 3A4, 3A5, 3A7, by contrast exhibit inducing properties when used concomitantly with steroid hormones.
- Herbal preparations containing St John's wort (Hypericum perforatum) may induce the metabolism of oestrogens via the CYP450 3A4 pathway.

Clinically, an increased metabolism of oestrogens 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.

Oestrogens have also been found to interact with the following drugs: Coumarins, lamotrigine, and selegiline.

At transdermal administration, the first-pass effect in the liver is avoided and, thus, transdermally applied oestrogens might be less affected than oral hormones by enzyme inducers.

Oestrogens might interfere with the metabolism of other drugs:
Oestrogens per se may inhibit CYP450 drug-metabolising enzymes via competitive inhibition. This is in particular to be considered for substrates with a narrow therapeutic index, such as

- tacrolimus and cyclosporine A (CYP450 3A4, 3A3)
- fentanyl (CYP450 3A4)
- theophylline (CYP450 1A2)

Clinically this may lead to a plasma increase of the affected substances up to toxic levels. Thus, careful drug monitoring for an extended period of time might be indicated and a dosage decrease of tacrolimus, fentanyl, cyclosporin A, and theophylline may be necessary.

Some laboratory tests can be influenced by oestrogens such as tests for thyroid function or glucose tolerance, (see Section 4.4).

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:

Elleste Solo MX 40 is not indicated during pregnancy. If pregnancy occurs during medication with Elleste Solo MX 40, treatment should be withdrawn immediately. The results of most epidemiological studies to date relevant to inadvertent foetal exposure to estrogens indicate no teratogenic or foetotoxic effects.

Lactation:

Elleste Solo MX 40 is not indicated during lactation.

4.7 Effects on ability to drive and use machines

Elleste Solo MX 40 has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Elleste Solo MX 40 is generally well tolerated. The most frequent side effects, (reported in 10 to 20 % of patients, on at least one occasion, in clinical trials with Elleste Solo MX 40) which do not normally prevent continued treatment include: breast tenderness, headaches and breakthrough bleeding. Some patients experience mild and transient local erythema at the site of application with or without itching; this usually disappears rapidly on removal of the patch. The overall incidence of general patch irritation in clinical studies is less than 5 %. In a clinical study 3 % of 102 patients showed well defined

erythema (Draize scale) 30 minutes after patch removal. No instances of permanent skin damage have been reported. If unacceptable topical side effects do occur discontinuation of treatment should be considered.

The following adverse reactions have been reported with Elleste Solo MX 40 and/or oestrogen therapy:

System Organ Class		Common ADRs ≥ 1/100, < 1/10	Uncommon >1/1,000, <1/100	Rare ADRs ≥ 1/10,000, < 1/1000		Frequency Not Known*
Infections and infestations			Vaginal candidiasis			
Immune system disorders			Hypersensitivity			
Neoplasms, benign, malignant and unspecified (incl. cysts and polyps)						Breast cancer[a]; Oestrogen dependent neoplasms benign and malignant, e.g. endometrial cancer[b], ovarian cancer[c]; Increase in size of leiomyoma
Metabolism and nutrition disorders		Weight increased, Weight decreased				
Psychiatric disorders			Depressed mood	Anxiety, Libido decreased, Libido increased		
Nervous system		Headache	Dizziness	Migraine		Probable

disorders						dementia over the age of 65 (see section 4.4); Chorea; Exacerbation of epilepsy
Eye disorders			Visual disturbances	Contact lens intolerance		
Cardiac disorders			Palpitations			
Vascular disorders						Stroke[f], Arterial thromboembolism, i.e. angina[e] and myocardial infarction[e]. For further information see sections 4.3 and 4.4. Venous thromboembolism[d], i.e. deep leg or pelvic venous thrombosis and pulmonary embolism. For further information see sections 4.3 and 4.4.
Gastrointestinal disorders		Abdominal pain; Nausea	Dyspepsia	Bloating, Vomiting		Pancreatitis (in women with pre-existing hypertriglyceridaemia); Gastroesophageal reflux

						disease
Hepatobiliary disorders			Gall bladder disorder			Hepatic function abnormal, sometimes with jaundice; Cholelithiasis;
Skin and subcutaneous tissue disorders		Rash, Pruritus	Erythema nodosum, Urticaria	Hirsutism, Acne		Angioedema; Chloasma; Erythema multiforme; Vascular purpura; ; Application site reactions: erythema with or without pruritus
Musculoskeletal and connective tissue disorders				Muscle cramps		
Renal and urinary disorders						Urinary incontinence
Reproductive system and breast disorders		Metrorrhagia, Uterine/vaginal bleeding including spotting	Breast pain, Breast tenderness	Dysmenorrhoea, Vaginal discharge, Breast enlargement. Premenstrual syndrome		Fibrocystic breast disease; Endometriosis;
General disorders and administration			Oedema	Fatigue		

site conditions						

*Undesirable effects from spontaneous post-marketing reporting sources, which have not been observed in clinical trials.

a **Breast cancer risk**

- An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking combined oestrogen-progestogen therapy for more than 5 years.
- The increased risk in users of oestrogen-only therapy is lower than that seen in users of oestrogen-progestogen 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 studies

Estimated 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-progestogen	
50	13.3	1.6	8.0

* 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.

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

Age at	Incidence per 1000 never-users of	Risk ratio	Additional cases per 1000 HRT

start HRT (years)	HRT over a 10 year period (50 – 59 years) *		users after 10 years
		Oestrogen-only HRT	
50	26.6	1.3	7.1
		Combined oestrogen-progestogen	
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 (yrs)	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)*2
		CEE+MPA oestrogen & progestogen‡	
50-79	17	1.2(1.0-1.5)	+4(0-9)

‡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.

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

b 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 progestogen 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)).

c Ovarian cancer risk

Use of oestrogen-only or combined oestrogen-progestogen 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.

d 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 HT (see section 4.4). Results of the WHI studies are presented: WHI Studies:

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 over 5 years
Oral oestrogen-only*3			
50-59	7	1.2 (0.6-2.4)	1 (-3-10)
Oral combined oestrogen-progestogen			
50-59	4	2.3 (1.2-4.3)	5 (1-13)

*3 Study in women with no uterus

e Risk of coronary artery disease

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

f Risk of ischaemic stroke

- The use of oestrogen-only and oestrogen + progestogen 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*4 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)

*4 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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

This is not likely due to the mode of administration. If it is necessary to stop delivery, then the patch can be removed and plasma estradiol levels will fall rapidly.

Nausea, vomiting, sleepiness, dizziness and withdrawal bleeding may occur in some women. There is no specific antidote and treatment should be symptomatic.

Aforementioned information is also applicable for overdosing in children.

The patch(es) should be removed.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group:
Natural and semisynthetic oestrogens, plain.
ATC Code G03CA03

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.

Relief of oestrogen-deficiency symptoms and bleeding patterns.
Relief of menopausal symptoms was achieved during the first few weeks of treatment.

5.2 Pharmacokinetic properties

Estradiol is absorbed from the patch across the stratum corneum and is delivered systemically at a low but constant rate throughout the period of application (3 to 4 days). The estimated delivery of estradiol is approximately 40 μg/day for Elleste Solo MX 40.

Steady state plasma estradiol concentrations have been demonstrated in the range from Cmin 34 pg/ml to Cmax 62 pg/ml for the Elleste Solo MX 40 patch (including baseline levels) and these are maintained throughout the dose interval (for up to four days). Absorption rate may vary between individual patients. After removal of the last patch plasma estradiol and estrone concentrations return to baseline values in less than 24 hours.

Estradiol is mainly metabolized in the liver. Its main metabolites are estriol, estrone, and their conjugates. The plasma half life of estradiol is 1-2 hours. Metabolic plasma clearance varies between 450-625 ml/min/m2. The metabolites are mainly excreted via the kidneys as glucuronides and sulphates. Oestrogens also undergo enterohepatic circulation.

5.3 Preclinical safety data

There are no preclinical safety data of relevance to the prescriber in the target population that are additional to those already included in other sections of the Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Diethyltoluamide
Acrylic adhesive (Butylacrylate/Butyl-methacrylate-copolymer-dispersion-Roderm™ MD-5600)
Acrylic emulsion (Acrylic-acid copolymer-dispersion - Roderm™ MD-6000)
Backing: Polyester film (Scotchpak 9733)
Release liner: Siliconised aluminised polyester

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5 Nature and contents of container

Sachet made out of laminate comprising of paper (clay coated), bonding layer of LDPE, aluminium foil and heat seal layer of LDPE.containing one transdermal patch. Each carton contains eight patches, sufficient for one 28 day cycle and a patient leaflet. An additional pack containing two patches may also be available.

6.6 Special precautions for disposal

Detailed instructions for use are provided in the patient leaflet.

7 MARKETING AUTHORISATION HOLDER

Exeltis Healthcare S.L.
Avda. de Miralcampo 7
Pol. Ind. Miralcampo, 19200-Azuqueca de Henares (Guadalajara)
Spain

8 MARKETING AUTHORISATION NUMBER(S)

PL 44081/0031

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12/03/2009

10 DATE OF REVISION OF THE TEXT

09/03/2025