Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Lenzetto 1.53 mg/spray, Transdermal Spray, Solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each spray delivers 90 microliter of transdermal spray, solution containing 1.53 mg of estradiol (equivalent to 1.58 mg of estradiol hemihydrate).

Excipient with known effect: each spray contains 65.47 mg ethanol.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Transdermal spray, solution.
The solution is clear, colourless to pale yellow.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Hormone Replacement Therapy (HRT) for oestrogen deficiency symptoms in postmenopausal women (in women at least 6 months since last menses or surgical menopause, with or without a uterus).

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

4.2 Posology and method of administration

Posology
Lenzetto is administered once daily, either as a monotherapy or as a continuous sequential treatment (when combined with a progestogen).

One metered-dose spray is administered once daily to the dry and healthy skin of the forearm as a starting dose. The dose may be increased to two metered-dose sprays daily to the forearm based on clinical response. Dose increase should be based on the degree of the woman's menopausal symptoms and should be made only after at least 4 weeks of continuous treatment with Lenzetto. The maximum daily dose is 3 metered-dose sprays (4.59 mg/day) to the forearm. Dose increase should be discussed with the physician. For patients who have difficulty applying the prescribed dose to distinct, non-overlapping areas of the same forearm, {Invented name} may also be applied to sites on the alternate forearm, or to sites on the inner thigh.

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.

When the degree of the woman's menopausal symptoms is not reduced after a dose increase, the patient should be back-titrated to the previous dose.

Patients should be re-evaluated periodically as clinically appropriate (e.g. 3-month to 6-month intervals) to determine if treatment is still necessary (see section 4.4).

When oestrogen is prescribed for a postmenopausal woman with a uterus, a progestagen approved for addition to oestrogen treatment should also be initiated to reduce the risk of endometrial cancer. Only progestagens approved for addition to oestrogen treatment should be administered.

In women with a uterus

In women with an intact uterus, the product should be combined with a progestagen approved for addition to oestrogen treatment in a continuous - sequential dosing scheme: the oestrogen is dosed continuously. The progestagen is added for at least 12 to 14 days of every 28-day cycle, in a sequential manner.

Advice on how to initiate treatment should be given for treatment naive patients and for patients changing from other HRTs (cyclic, sequential or continuous combined).
In the period in which the oestrogen is combined with the progestagen, a withdrawal bleeding can occur. A new 28-day treatment cycle is started without a break.

In women without a uterus
Unless there is a previous diagnosis of endometriosis, it is not recommended to add progestagen for women without a uterus.

Overweight and obese women
There is some limited data that the rate and extent of absorption of Lenzetto can be reduced in overweight and obese women. During the treatment, the dose of Lenzetto may require adjustment. Dose modification should be discussed with the physician.

Paediatric population
There is no relevant use of Lenzetto in the paediatric population.

Missed dose
If a dose is missed, the patient should make up for the missed dose as soon as she remembers and take the next dose at the usual time. If it is almost time for the next dose, she should skip the missed dose and take the next dose at the usual time. If one or more doses are missed one primer spraying with the cover on is needed. Forgetting a dose may increase the likelihood of breakthrough bleeding and spotting.

Method of administration
The container should be held upright and vertical for spraying. Before a new applicator is used for the first time, the pump should be primed by spraying three times into the cover.

The daily dose is one metered-dose spray on the inner forearm. If two or three sprays are prescribed as the daily dose, they should be applied to adjacent non-overlapping (side-by-side) 20 cm^2 areas on the inner surface of the arm between the elbow and the wrist and allowed to dry for approximately 2 minutes. Women should cover the application site with clothing if another person may come into contact with that area of skin after the spray dries. The site of application should not be washed for 60 minutes. Do not allow another person to touch the site of application within 60 minutes of application.

Patients should be informed that children should not come in contact with the area of the body where estradiol spray was sprayed on (see section 4.4). If a child comes in contact with the part of the arm where Lenzetto was sprayed on, the child's skin should be washed with soap and water as soon as possible.

Studies suggest that compared to applying it to the inner surface of the forearm, absorption of estradiol is similar when Lenzetto is applied to the skin of the thigh, but is lower when applied to the skin of the abdomen.

If the product is used according to the instructions, irrespective of different spray shape or pattern on the skin each puff will deliver the same amount of ingredient on the skin.

Elevated skin temperature
The effect of increased ambient temperature with Lenzetto has been studied and clinically relevant difference in the extent of absorption of Lenzetto was not observed. However, Lenzetto should be use with caution in extreme temperature conditions, such as sun bathing or sauna.

Application of sunscreen
When sunscreen is applied about one hour following Lenzetto, estradiol absorption may be decreased by 10%. When sunscreen was applied about one hour prior to Lenzetto, no effect on absorption was observed (see section 5.2).

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;
- Porphyria;
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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.

Conditions which need supervision

If any of the following conditions are present, have occurred previously, and/or have been aggravated during pregnancy or previous hormone treatment, the patient should be closely supervised. It should be taken into account that these conditions may recur or be aggravated during treatment with Lenzetto, in particular:

- Leiomyoma (uterine fibroids) or endometriosis
- Risk factors for thromboembolic disorders (see below)
- Risk factors for oestrogen-dependent tumours, e.g. first-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

Reasons for immediate withdrawal of therapy

Therapy should be discontinued in case a contraindication is discovered and in the following situations:

- Jaundice or deterioration in liver function
- Significant increase in blood pressure
- New onset of migraine-type headache
- Pregnancy

Endometrial hyperplasia and carcinoma

In women with an intact uterus, the risk of endometrial hyperplasia and carcinoma is increased when oestrogens are administered alone for prolonged periods. The reported increase in endometrial cancer risk among oestrogen-only users varies

from 2-to 12-fold greater compared with non-users, depending on the duration of treatment and oestrogen dose (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.

For Lenzetto, the endometrial safety of added progestagens has not been studied.

Break-through bleeding and spotting may occur during the first months of treatment. If break-through 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 progestagens to oestrogen replacement therapy should be considered in women who have undergone hysterectomy because of endometriosis if they are known to have residual endometriosis.

Breast cancer
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 the 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 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 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 must 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 therapy
Randomised controlled data found no increased risk of CAD in hysterectomised women using oestrogen-only therapy.

Ischaemic stroke
Combined oestrogen-progestagen and oestrogen-only therapy are associated with an up to 1.5-fold increase in risk of ischaemic stroke. The relative risk does not change with age or time since menopause. However, as the baseline risk of stroke is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age (see section 4.8).

Visual abnormalities
Retinal vascular thrombosis has been reported in women receiving oestrogens. Medication must be discontinued immediately, pending examination if there is sudden partial or complete loss of vision, or a sudden onset of proptosis, diplopia, or migraine. If examination reveals papilledema or retinal vascular lesions, oestrogens should be permanently discontinued.

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.

Other conditions
Oestrogens may cause fluid retention, and therefore patients with cardiac or renal dysfunction should be carefully observed.

Exogenous oestrogens may induce or exacerbate symptoms of hereditary and acquired angioedema.

Women with pre-existing hypertriglyceridemia 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.

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-I-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.

Application of sunscreen
When sunscreen is applied about one hour following Lenzetto, estradiol absorption may be decreased by 10%. When sunscreen was applied about one hour prior to Lenzetto, no effect on absorption was observed (see section 5.2).

Elevated skin temperature
The effect of increased ambient temperature has been studied and approximately 10% difference was observed in the absorption of Lenzetto. This effect is not expected to be of clinical relevance for daily administration of Lenzetto (see section 5.2). Nevertheless, Lenzetto should be used with caution in extreme temperature conditions, such as sunbathing or sauna.

Paediatric population
Potential estradiol transfer to children
Estradiol spray can be accidentally transferred to children from the area of the skin where it was sprayed on.

Post-marketing reports of breast budding and breast masses in prepubertal females, precocious puberty, gynaecomastia and breast masses in prepubertal males following unintentional secondary exposure to estradiol spray have been reported. In most cases, the condition resolved with removal of estradiol exposure.

Patients should be instructed:
- not to allow others, especially children, to come into contact with the exposed area of the skin and to cover the application site with clothing if needed. In case of contact, the child's skin should be washed with soap and water as soon as possible.
- to consult a physician in case of signs and symptoms (breast development or other sexual changes) in a child that may have been exposed accidentally to estradiol spray.

In case of the possibility of unintentional secondary exposure to Lenzetto, the physician should identify the cause of abnormal sexual development in the child. If unexpected breast development or changes are determined to be the result of unintentional exposure to Lenzetto, the physician should counsel the woman on the appropriate use and handling of Lenzetto when around children. Consideration should be given to discontinuing Lenzetto if conditions for safe use cannot be met.

Excipient
This medicine contains 65.47 mg of alcohol (ethanol) in each dose which is equivalent to 72.74%w/v. It may cause burning sensation on damaged skin.
Alcohol-based products are flammable. Keep away from fire. While using the device, open flame, lit cigarette or use of some hot devices (e.g. hairdryers) should be avoided, until the spray has dried on the skin.

4.5 Interaction with other medicinal products and other forms of interaction

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

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

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).

No interaction studies have been conducted for Lenzetto.

4.6 Fertility, pregnancy and lactation

Pregnancy
Lenzetto is not indicated during pregnancy. If pregnancy occurs during medication with Lenzetto treatment should be withdrawn immediately.
The results of most epidemiological studies to date relevant to inadvertent foetal exposure to oestrogens indicate no teratogenic or foetotoxic effects.

Breast-feeding
Lenzetto is not indicated during lactation.

4.7 Effects on ability to drive and use machines

No studies of the effects of Lenzetto on the ability to drive and use machines have been performed.

4.8 Undesirable effects

In a 12-week, randomised, placebo-controlled trial of Lenzetto in 454 women, 80-90% of women who were randomised to active substance received at least 70 days of therapy and 75-85% of the women who were randomised to placebo received at least 70 days of therapy.

The adverse events are listed by organ class and frequency according to MedDRA frequency convention: Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000).

Table 1: Adverse Events Reported

System Organ Class (MedDRA 12.0)	Common (≥1/100 to <1/10)	Uncommon (≥1/1000 to <1/100)	Rare (≥1/10,000 to <1/1,000)
Immune system disorders		Hypersensitivity reaction	
Psychiatric disorders		Depressed mood, Insomnia	Anxiety, Libido decreased, Libido increased

Nervous system disorders	Headache	Dizziness	Migraine
Eye disorder		Visual disturbances	Contact lens intolerance
Ear and labyrinth disorders		Vertigo	
Cardiac disorders		Palpitations	
Vascular disorders		Hypertension	
Gastrointestinal disorders	Abdominal pain, Nausea	Diarrhoea, Dyspepsia	Bloating, Vomiting
Skin and subcutaneous tissue disorders	Rash, Pruritus	Erythema nodosum, Urticaria, Skin irritation	Hirsutism, Acne
Musculoskeletal and connective tissue disorders		Myalgia	Muscle spasms
Reproductive system and breast disorders	Breast pain, Breast tenderness, Uterine/Vaginal bleeding including spotting, Metrorrhagia	Breast discolouration, Breast discharge, Cervical polyp, Endometrial hyperplasia, Ovarian cyst, Vaginitis	Dysmenorrhoea, Premenstrual-like syndrome, Breast enlargement
General disorders and administration site condition		Oedema, Axillary pain	Fatigue
Investigations	Weight increased, Weight decreased	Gamma-glutamyltransferase increased, Blood cholesterol increased	

From post-marketing surveillance additionally, the following adverse events have been reported:
Skin and subcutaneous tissue disorders

- Alopecia
- Chloasma
- Skin discolouration

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 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 1,000 never-users of HRT over a 5-year period (50 – 54 years)***	**Risk ratio**	**Additional cases per 1,000 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/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 start HRT (years)	**Incidence per 1,000 never-users of HRT over a 10-year period (50 – 59 years)***	**Risk ratio**	**Additional cases per 1,000 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 1,000 women in placebo arm over 5 years**	**Risk ratio & 95%CI**	**Additional cases per 1,000 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 & progestagen‡	
50-79	17	1.2 (1.0-1.5)	+4 (0-9)

*[2] 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.
CEE – Conjugated equine oestrogen
MPA – Medroxiprogesteron acetate

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
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 2,000 users. In women aged 50 to 54 who are not taking HRT, about 2 women in 2,000 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 HT (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 1,000 women in placebo arm over 5-years**	**Risk ratio and 95%CI**	**Additional cases per 1,000 HRT users**
Oral oestrogen-only[3]			
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)

3 *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[4] over 5-years' use

Age range (years)	**Incidence per 1,000 women in placebo arm over 5-years**	**Risk ratio and 95%CI**	**Additional cases per 1,000 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.*

The following additional adverse reactions have also been reported with oestrogen and/or progestin therapy: angioedema, anaphylactoid/anaphylactic reactions, glucose intolerance, mental depression, mood disturbances, irritability, exacerbation of chorea, exacerbation of epilepsy, dementia (see section 4.4), exacerbation of asthma, cholestatic jaundice, increased incidence of gallbladder disease, pancreatitis, enlargement of hepatic haemangiomas, chloasma or melasma, that may persist when drug is discontinued; erythema multiforme, haemorrhagic eruption, loss of scalp hair, arthralgias, galactorrhoea, fibrocystic breast

changes, increase in size of uterine leiomyomata, change in amount of cervical secretion, changes in cervical ectropion, vaginal candidiasis, hypocalcaemia (preexisting condition).

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 HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

Effects have not been reported following acute ingestion of large doses of oestrogen-containing products. Overdosage of oestrogen may cause nausea and vomiting, breast tenderness, dizziness, abdominal pain, drowsiness/fatigue, and withdrawal bleeding may occur in women. Treatment of overdose consists of discontinuation of Lenzetto together with institution of appropriate symptomatic care.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sex hormones and modulators of the genital system, Oestrogens, Natural and semisynthetic oestrogens, plain; Estradiol, ATC Code: G03CA03

Lenzetto provides systemic oestrogen replacement therapy by releasing estradiol, the major oestrogenic hormone secreted by the ovaries. 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.

5.2 Pharmacokinetic properties

Absorption
When Lenzetto was applied to the skin, the average drying time was 90 sec (median = 67 sec).
In a multiple-dose study, postmenopausal women were treated for 14 days with one-, two- or three-90 microliter sprays of Lenzetto on the inner forearm. Serum concentrations of estradiol appeared to reach a steady state after 7-8 days of application of Lenzetto.
Following morning administration, blood levels remained relatively stable and within the therapeutic range throughout the 24-hour period following administration with peak levels between 2 AM and 6 AM.

In a clinical study, postmenopausal women were treated for 12 weeks with one, two or three 90 microliter sprays of Lenzetto on the inner forearm and blood levels of estradiol were measured at Week 4, 8 and 12. The estradiol exposure increased with increasing dose (one, two, three sprays respectively) but the increase was slightly less than proportional to dose.
Pharmacokinetic parameters for estradiol and estrone from one, two or three 90 microliter sprays of Lenzetto were further examined in a clinical study and are described in Table 2.

Table 2. Pharmacokinetic parameters on Day 14 (Unadjusted for Baseline)

PK Parameter[1]	**Number of Daily Sprays of Lenzetto**		
	1 Spray (N = 24)	**2 Spray (N = 23)**	**3 Spray (N = 24)**
Estradiol (pg/mL)			
Cmax	31.2	46.1	48.4
Cmin	10.3	16.4	18.9
Cavg	17.8	28.2	29.5
Estrone (pg/mL)			
Cmax	47.1	58.4	67.4
Cmin	29.0	39.0	44.1
Cavg	35.5	48.7	54.8
[1] All values expressed are geometric means.			

A second pharmacokinetic study assessed serum estradiol concentrations in 20 postmenopausal women treated for 18 days with three 90 microliter sprays of Lenzetto on the inner forearm. In this study, application of sunscreen one hour prior to the application of Lenzetto caused no significant difference in absorption of estradiol. When sunscreen was applied one hour after the application of Lenzetto, there was approximately a 10% decrease in the absorption of estradiol (see section 4.4).

Studies suggest that compared to applying it to the inner surface of the forearm, absorption of estradiol is similar when Lenzetto is applied to the skin of the thigh, but is lower when applied to the skin of the abdomen.

Estradiol transfer during administration of Lenzetto
In a clinical trial 20 postmenopausal women who were treated with three 90 microliter sprays of estradiol transdermal spray (1.53 mg/spray) to their inner forearm once daily were assessed for transfer risk, by holding their forearm to the inner forearm of a male for 5 minutes an hour after treatment. During the clinical study no significant transfer of estradiol was observed. Information on the transfer within one hour is not available (see section 4.4).

Elevated skin temperature
A bioavailability study assessed the effect of increased ambient temperature in 24 healthy postmenopausal women with 2 sprays on the forearm. In this study increased ambient temperature of 35 °C for 4 hours caused similar rate and extent of absorption with approximately 10% differences compared to data obtained at room temperature.

Overweight and obese women
To evaluate the influence of obesity on the absorption, a single-dose, comparative bioavaliability study was carried out. The study was performed to compare the rate and extent of absorption of Estradiol 1.53 mg/spray (90 microliter) in obese and normal weight women under normal temperature conditions after application of two sprays on the forearm. Based on the point estimates of baseline corrected unconjugated estradiol and unconjugated estrone, the extent and rate of absorption are approximately 33-38% and 15-17% lower while the median peak of absorption is observed 12 to 14 hours earlier. For baseline corrected total estrone, the extent and rate of absorption are approximately 7% lower and approximately 22% higher respectively, in obese post-menopausal females. The T_{max} is delayed by approximately 6 hours in obese post-menopausal females for this analyte.

Distribution
Oestrogens circulate in blood largely bound to sex hormone binding globulin (SHBG) and albumin.

Biotransformation
Estradiol is converted reversibly to estrone, and both can be converted to estriol, which is the major urinary metabolite. Oestrogens also undergo enterohepatic recirculation via sulfate and glucuronide conjugation in the liver, biliary secretion of conjugates into the intestine, and hydrolysis in the gut followed by reabsorption. In postmenopausal women, a significant proportion of the circulating oestrogens exist as sulfate conjugates, especially estrone sulfate, which serves as a circulating reservoir for the formation of more active oestrogens.

Elimination
Estradiol, estrone and estriol are excreted in the urine along with glucuronide and sulfate conjugates. Serum concentrations of estradiol, estrone and estrone sulfate returned to baseline levels in more than one week after discontinuation of therapy once steady-state had been achieved.

5.3 Preclinical safety data

Conventional studies of general toxicity data revealed no additional risks in addition to what has already been reflected in the SmPC. Long-term continuous administration of natural and synthetic oestrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testes and liver (see section 4.4).

Animal studies with estradiol or estradiol valerate have shown embryolethal effects even at relatively low doses; malformation of urogenitalia and feminisation of male foetuses.

Octisalate is included in the formulation as an excipients to enhance skin penetration. Octisalate has been widely used in commercial dermal products for many years. Despite the absence of many formal toxicity studies, octisalate is unlikely to represent any special hazard for humans as both the acute oral toxicity of octisalate and that the subchronic toxicity following dermal or oral route of administration are low. Tests for photo-toxicity and photo-contact allergy in man were negative.

Furthermore, tests for mutagenicity, clastogenicity, photo-mutagenicity and photo-clastogenicity, using bacterial and tissue culture tests systems were negative.

An effect of octisalate on human reproduction or carcinogenic actions are unlikely based on the hormone activity and genotoxicity studies conducted and bearing in mind the limited dermal penetration of octisalate, the relatively small dose of octisalate in the product (8.5%) and the absence of any reported effects from the extensive human use in sunscreens and cosmetics.

Environmental risk assessment studies have shown that the active ingredient estradiol hemihydrate may pose a risk for aquatic environment, especially for fish.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Octisalate
Ethanol 96%

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.
Use within 56 days of first use.

6.4 Special precautions for storage

Do not refrigerate or freeze.
Do not store above 25°C.
Contains ethanol which is flammable. Store away from heaters, open flames, and other sources of ignition.

6.5 Nature and contents of container

The solution is packaged in a glass vial fitted with a metered dose pump. The unit is encased in a plastic housing with a conical bell opening that controls the distance, angle, and area of application of the metered dose spray.

One container is filled with 6.5 mL, transdermal spray solution and is designed to deliver 56 sprays after priming.

Pack sizes:
One plastic container 6.5 mL (56 sprays)
Three plastic containers 3x6.5 mL (3x56 sprays)

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

After delivery of 56 sprays, the container must be discarded even if there is some leftover solution in it. The number of sprays made should be marked using the table on the carton. As drug residue will remain in the used up containers, they should not be disposed of via household waste. Empty containers should be returned to the pharmacy for destruction.
This medicinal product may pose a risk to the environment (see section 5.3).

7 MARKETING AUTHORISATION HOLDER

Gedeon Richter Plc
Gyömroi út 19-21
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Hungary

8 MARKETING AUTHORISATION NUMBER

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