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Public Assessment Report

Name of the Product:

Lenzetto 1.53 mg/spray

transdermal spray, solution

(estradiol)

Procedure number: HU/H/0361/001/DC

Marketing authorisation holder: Gedeon Richter Plc.

Date: 3 September 2015

CONTENT

LAY SUMMARY

After careful assessment of its quality and therapeutic benefit/risk ratio, the member states have granted the marketing authorisation of the Lenzetto 1.53 mg/spray transdermal spray, solution. The holder of the marketing authorisation is Gedeon Richter Plc. in the Reference Member State.

The active ingredient is estradiol (as estradiol hemihydrate). Each spray contains 1.53 mg estradiol (equivalent to 1.58 mg estradiol hemihydrate).

The other ingredients are octisalate and ethanol 96%.

Lenzetto is a transdermal spray containing a solution of estradiol and octisalate in ethanol. It is provided with a metered dose pump and is supplied as a plastic container with a plastic cover. There is a glass container inside. Each pack contains one container which is filled with 8.1 ml of solution and is designed to deliver 56 sprays.

Lenzetto is for Hormone Replacement Therapy (HRT). It contains a female hormone, from the group of estrogens. It is used in postmenopausal women with at least 6 months since their last natural period.

Lenzetto can also be used in women who have had surgery to remove their ovaries as this causes instant menopause.

Lenzetto is a spray solution which contains small amounts of a medicine called estradiol. When sprayed onto the skin as directed, it passes through the skin into your bloodstream.

Lenzetto is used for relief of symptoms occurring after menopause.

> During the menopause, the amount of the oestrogen produced by a woman's body drops. This can cause symptoms such as hot face, neck and chest ("hot flushes"). Lenzetto alleviates these symptoms after menopause. The patients will only be prescribed this medicine if the symptoms seriously hinder the daily life.

Lenzetto is also indicated to treat oestrogen deficiency symptoms after menopause; when menstruation has ceased following menopause. Symptoms of oestrogen deficiency include hot flushes (sudden waves of heat and sweating in the whole body), sleeping problems, irritability and dryness of the vagina.

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

It is important that Lenzetto is not a contraceptive.

What patients need to know before using Lenzetto?

Medical history and regular check-ups

The use of HRT carries risks which need to be considered when deciding whether to start using it, or whether to carry on using it.

The experience in treating women with a premature menopause (due to ovarian failure or surgery) is limited. If the patient has a premature menopause the risks of using HRT may be different. The doctor should be informed accordingly.

Before starting (or restarting) HRT, the doctor will ask the patient about her own and her family's medical history. The doctor may decide to perform a physical examination. This may include an examination of the breasts and/or an internal examination, if necessary.

Once have started on Lenzetto, the patient should see the doctor for regular check-ups (at least once a year). At these check-ups, the benefits and risks of continuing with Lenzetto should be discussed with the doctor.

Patients should go for regular breast screening, as recommended by their doctor.

Patients should not use Lenzetto if any of the following applies. Moreover, if any of the following conditions appear for the first time while using Lenzetto, its use must be stopped at once and the doctor consulted immediately. If the patient

- has or ever had breast cancer**,** or if it is suspected;
- has or ever had any cancer which is sensitive to oestrogens, such as cancer of the lining of the womb (*endometrium*), or if is suspected;
- has any unexplained vaginal bleeding;
- has excessive thickening of the lining of the womb (*endometrial hyperplasia*) that is not being treated;
- has or ever had a blood clot in the vein (*thrombosis*), such as in the legs (*deep venous thrombosis*) or the lungs (*pulmonary embolism*);
- has a blood clotting disorder (such as protein C, protein S or antithrombin deficiency);
- has, or recently had a disease caused by blood clots in the arteries, such as heart attack, stroke or angina;
- has, or ever had a liver disease and her liver function tests have not returned to normal;
- has a rare blood problem called "porphyria" which passes down in families (is inherited);
- is allergic to estradiol or any of the other ingredients of this medicine.

Warnings and precautions

Patients should tell your doctor if they have or ever had any of the following problems, before starting the treatment, as these may return or become worse during treatment with Lenzetto. (If it happens, the doctor should be visited more often for check-ups):

- fibroids inside the womb;
- growth of womb lining outside the womb (endometriosis) or a history of excessive growth of the womb lining (endometrial hyperplasia);
- increased risk of developing blood clots;
- increased risk of getting an oestrogen-sensitive cancer (such as having a mother, sister or grandmother who has had breast cancer);

- high blood pressure;
- a liver disorder such as a benign liver tumour;
- diabetes;
- gallstones;
- migraine or severe headache;
- a disease of the immune system that affects many organs of the body (systemic lupus erythematosus, SLE);
- epilepsy;
- asthma;
- a disease affecting the eardrum and hearing (otosclerosis);
- a very high level of fat in the blood (triglycerides);
- fluid retention due to cardiac or kidney problems.

Patients should stop using Lenzetto and see a doctor immediately if noticing any of the following when using HRT:
- any of the conditions mentioned in the "Patients should not use Lenzetto" section;
- yellow discolouration on the skin or the whites of the eyes (jaundice). These may be signs of a liver disease;
- a large rise in the blood pressure (symptoms may be headache, tiredness, dizziness);
- migraine-like headaches which happen for the first time;
- if becoming pregnant;
- noticing signs of a blood clot, such as:
  - painful swelling and redness of the legs;
  - sudden chest pain;
  - difficulty in breathing.

Note: Lenzetto is not a contraceptive. If it is less than 12 months since the last menstrual period or the patient is less than 50 years old, she may still need to use additional contraception to prevent pregnancy.

HRT and cancer

Using oestrogen-only HRT will increase the risk of excessive thickening of the lining of the womb (endometrial hyperplasia) and cancer of the womb lining (endometrial cancer).

Taking a progestogen in addition to the oestrogen for at least 12 days of each 28 day cycle protects the patient from this extra risk. Thus, the doctor will prescribe a progestogen separately if the patient still has her womb. If the womb has been removed (a hysterectomy), it must be discussed with the doctor whether this product can be taken safely without a progestogen.

In women who still have a womb and who are not using HRT, on average, 5 in 1000 will be diagnosed with endometrial cancer between the ages of 50 and 65.

For women aged 50 to 65 who still have a womb and who take oestrogen-only HRT, between 10 and 60 women in 1000 will be diagnosed with endometrial cancer (i.e. between 5 and 55 extra cases), depending on the dose and for how long it has been taken.

Lenzetto contains a higher dose of estrogens than other estrogen-only HRT products. The risk of endometrium cancer when using Lenzetto together with a progestogen is not known.

Unexpected bleeding

The patients will have a bleed once a month (so-called withdrawal bleed) while using Lenzetto if it is combined with sequentially dosed progestagen product. But, if they have unexpected bleeding or drops of blood (spotting) besides your monthly bleeding, which:
- carries on for more than the first 6 months;
- starts after Lenzetto has been used for more than 6 months;
- carries on after using Lenzetto has been terminated

the doctor should be consulted as soon as possible.

Breast cancer

Evidence suggests that using combined oestrogen-progestogen and possibly also oestrogen-only HRT increases the risk of breast cancer. The extra risk depends on how long HRT has been taken. The additional risk becomes clear within a few years. However, it returns to normal within a few years (at most 5) after stopping treatment.

For women who have had their womb removed and who are using oestrogen-only HRT for 5 years, little or no increase in breast cancer risk is shown.

Women aged 50 to 79 who are not using HRT, on average, 9 to 14 in 1000 will be diagnosed with breast cancer over a 5-year period. For women aged 50 to 79 who are using oestrogen-progestogen HRT over 5 years, there will be 13 to 20 cases in 1000 users (i.e. an extra 4 to 6 cases).

The breasts must be checked regularly. If noticing any of the following changes the doctor must be consulted:
- dimpling of the skin;
- changes in the nipple;
- any lumps that can be seen or felt.

Additionally, patients are advised to join mammography screening programs when offered. For mammogram screening, it is important to inform the nurse/healthcare professional who is actually taking the x-ray on the use of HRT, as this medication may increase the density of the breasts which may affect the outcome of the mammogram. Where the density of the breast is increased, mammography may not detect all lumps.

Ovarian cancer

Ovarian cancer is rare. A slightly increased risk of ovarian cancer has been reported in women using HRT for at least 5 to 10 years.

Women aged 50 to 69 who are not using HRT, on average about 2 women in 1000 will be diagnosed with ovarian cancer over a 5-year period. For women who have been using HRT for 5 years, there will be between 2 and 3 cases per 1000 users (i.e. up to 1 extra case).

Effect of HRT on heart and circulation

The risk of blood clots in the veins (thrombosis) is about 1.3 to 3-times higher in HRT users than in non-users, especially during the first year of using it.

Blood clots can be serious, and if one travels to the lungs, it can cause chest pain, breathlessness, fainting or even death.

Patients are more likely to get a blood clot in the veins as getting older and if any of the following applies (in the latter case the doctor should be informed):
- inability to walk for a long time because of major surgery, injury or illness;
- serious overweight (BMI >30 kg/m^2);
- having any blood clotting problem that needs long-term treatment with a medicine used to prevent blood clots;
- any of the close relatives has or ever had a blood clot in the leg, lung or another organ;
- systemic lupus erythematosus (SLE);
- having cancer.

Looking at women in their 50s who are not using HRT, on average, over a 5-year period, 4 to 7 in 1000 would be expected to get a blood clot in a vein.

For women in their 50s who have been using oestrogen-progestogen HRT for over 5 years, there will be 9 to 12 cases in 1000 users (i.e. an extra 5 cases).

For women in their 50s who have had their womb removed and have been using oestrogen-only HRT for over 5 years, there will be 5 to 8 cases in 1000 users (i.e. 1 extra case).

Heart disease (heart attack)

There is no evidence that HRT will prevent a heart attack.

Women over the age of 60 years who use oestrogen-progestogen HRT are slightly more likely to develop heart disease than those not using any HRT.

For women who have had their womb removed and are using oestrogen-only therapy there is no increased risk of developing a heart disease.

Stroke

The risk of getting stroke is about 1.5 times higher in HRT users than in non-users. The number of extra cases of stroke due to use of HRT will increase with age.

Looking at women in their 50s who are not using HRT, on average, 8 in 1000 would be expected to have a stroke over a 5-year period. For women in their 50s who are using HRT, there will be 11 cases in 1000 users, over 5 years (i.e. an extra 3 cases).

Other conditions

HRT will not prevent memory loss. There is some evidence of a higher risk of memory loss in women who start using HRT after the age of 65. Speak to your doctor for advice.

Children

The estrogen in Lenzetto spray can be accidentally transferred to other people from the area of skin where it was sprayed on. Others, especially children, should not be allowed to come into contact with the exposed area of the patient's skin. If a child comes in contact with the part of the arm where Lenzetto was sprayed, the child's skin must be washed with soap and water as soon as possible. Young children who accidentally came into contact with the area where Lenzetto was sprayed on, may show signs of puberty that are not expected (for example, breast budding). The healthcare provider must be called right away if any signs and symptoms (breast development or other sexual changes) in a child that may have occurred through accidental exposure to Lenzetto might be seen. In most cases the child's breasts will go back to normal when they are no longer exposed to Lenzetto.

Pets

Pets should not be allowed to lick or touch the arm where Lenzetto was sprayed. Small pets may be especially sensitive to the estrogen contained in it.

If a pet exhibits mammary/nipple enlargement and/or vulvar swelling, or any other sign of illness, a veterinary surgeon should be contacted.

Other medicines and Lenzetto

Patients who are using, have recently used or might use any other medicines may inform their doctor accordingly.

Some medicines may interfere with the effect of Lenzetto. This might lead to irregular bleeding. This applies to the following medicines:
- medicines for epilepsy (such as phenobarbital, phenytoin and carbamazepine)
- medicines for tuberculosis (such as rifampicin, rifabutin);
- medicines for HIV infection (such as nevirapine, ritonavir, nelfinavir or efavirenz)
- (traditional) herbal medicines containing St John's Wort (*Hypericum perforatum*).

Laboratory Tests

Patients who need a blood test, tell their doctor or the laboratory staff that they are using Lenzetto because this medicine can affect the results of some tests.

Pregnancy and breast-feeding

Those who are pregnant or breast-feeding, think they may be pregnant or are planning to have a baby, ask their doctor for advice before taking this medicine.

Lenzetto is for post-menopausal women exclusively. If the patient becomes pregnant, using Lenzetto must be terminated immediately and the doctor contacted.

During breast-feeding Lenzetto should not be used.

Driving and using machines

Lenzetto has no known effect on the ability to drive or use machines.

Lenzetto contains alcohol

Alcohol-based liquids are flammable. Fire, flame or smoking until the spray has dried should be avoided.

How to use Lenzetto

The doctor will aim to prescribe the lowest dose to treat the symptoms for as short as necessary. During the treatment the doctor may adjust the dose according to the individual needs.

For patients having mot had a hysterectomy, the doctor will give tablets containing another hormone called progestogen to offset the effects of estrogens on the lining of the womb. The doctor will explain how to take these tablets. Withdrawal bleeding may occur at the end of the progestogen treatment period.

Where to apply Lenzetto

The spray should be applied to the inner forearm. It should not be applied to the breasts or any area near to the breasts

How to apply Lenzetto

Before spraying the first dose from a new container onto the dry and healthy skin, the applicator should be prepared for use by spraying three times with the cover on.

This, and the application is described with Figures in the package leaflet in detail.

Lenzetto should not be used on broken or damaged skin and it should not be massaged or rubbed into the skin.

Other people should not be allowed to touch the area of skin that have been sprayed for at least 60 minutes afterwards. If another person (special care for children) accidentally touches

the area of the skin where Lenzetto has been sprayed, this person must be urged to wash the area of the skin with soap and water right away.

How much Lenzetto should be used?

The doctor will probably start on the lowest dose (one spray per day) and the patient should talk with the doctor about how well the medicine is working. If necessary, the doctor may increase the dose to two sprays per day. The maximum daily dose is 3 sprays.

How often Lenzetto will be used?

The total number of sprays (dose(s)) that the doctor has prescribed should be applied at the same time each day.

The period of time the patient will continue to use Lenzetto

The doctor should be consulted every 3-6 months about how this medicine should be used. It should only be used for as long as it is needed to provide relief from hot flushes associated with menopause.

Other useful information

Sunscreens can alter the absorption of estrogen from Lenzetto.

The use of sunscreens on the part of the skin where Lenzetto is intended to be sprayed should be avoided for at least 1 hour before or after using Lenzetto.

Lenzetto should be used with caution under extreme temperature conditions, such as sauna or sunbathing.

There is limited data suggesting that the rate and extent of absorption of Lenzetto can be reduced in overweight and obese women but the doctor should be consulted. During the treatment the doctor may adjust the dose according to the individual needs.

What to do if more Lenzetto has been used then it should be?

If it is the case, or if children have been using the medicine by accident, the doctor or the hospital must be contacted to get an opinion of the risk and advice on action to be taken.

When using more Lenzetto than it should have been, patients feel sick, vomit and have withdrawal bleeding (unusual vaginal bleeding).

What to do if using Lenzetto was forgotten?

If using Lenzetto at its normal time was forgotten, it should be sprayed on as soon as the patient remembers it, and then use it normally on the next day. If it is almost time for the next

dose, just wait and apply the next dose as you normally would. No double dose must be used to make up for a forgotten dose.

What happens if a patient stops using Lenzetto?

The doctor will also explain how to stop using this medicine when the treatment is finished.

If the patient needs to have surgery

If the patient is are going to have surgery, the surgeon must be informed on the use of Lenzetto. Its use may need to be stopped about 4 to 6 weeks before the operation to reduce the risk of a blood clot. The doctor should be consulted about when the treatment with Lenzetto may be started again.

Possible side effects

Like all medicines, Lenzetto can also cause side effects, although not everybody experiences them.

The following diseases are reported more often in women using HRT compared to women not using it:
- breast cancer;
- abnormal growth or cancer of the lining of the womb (endometrial hyperplasia or cancer);
- ovarian cancer;
- blood clots in the veins of the legs or lung (venous thromboembolism);
- heart attack;
- stroke;
- gallbladder disease;
- high blood pressure;
- liver problems;
- high blood sugar;
- probable memory loss if HRT is started over the age of 65.

Some side effects can be serious. The following symptoms need immediate medical attention:
- sudden chest pain;
- pain in the chest that spreads to the arm or neck;
- breathing difficulties;
- painful swelling and redness in the legs;
- yellowing of the eyes and face (jaundice);
- unexpected vaginal bleeding (breakthrough bleeding) or spotting after using Lenzetto for some time or after you stop treatment;
- breast changes including dimpling of the breast skin, changes in the nipple, lumps that can be seen or felt;
- painful menstrual periods;

- dizziness and faintness;
- changes in speech;
- changes in vision;
- unexplained migraine-like headaches.

The following side effects below have been reported with Lenzetto

Common side effects (that may affect up to 1 in 10 people): headache, abdominal pain, nausea, rash, pruritis (itching), irregular uterine bleeding or vaginal bleeding including spotting, weight increase or weight decrease.

Uncommon side effects that (may affect up to 1 in 100 people): hypersensitivity reactions, depressed mood, insomnia (difficulty sleeping), dizziness, vertigo (feeling of dizziness or "spinning"), visual disturbances, palpitations (feeling the heartbeat), diarrhoea, dyspepsia (indigestion), increased blood pressure, erythema nodosum (characterized by painful reddish skin nodules), hives (general or localised rash or lumps), skin irritation, swelling due to fluid retention (oedema), muscle pain, breast tenderness, breast pain, breast discolouration, breast discharge, polyps (small growths) in the uterine or cervix, endometrial hyperplasia, ovary cyst, inflammation of genitals (vaginitis), increased liver enzymes and blood cholesterol, underarm pain.

Rare side effects (that may affect up to 1 in 1000 people): anxiety, decrease or increase in sexual drive, migraine, intolerance to contact lenses, bloating, vomiting, increased body hair, acne, muscle cramps, painful menstruation, vaginal bleeding, premenstrual like syndrome, breast enlargement, fatigue.

Other side effects, with frequency "not known" (cannot be calculated from the data) have been reported with Lenzetto during post-marketing surveillance: hair loss (alopecia), chloasma (golden brown pigment patches, so called "pregnancy patches", especially on the face), skin discolouration.

The following side effects have been reported with other HRT-s: serious allergic reaction which causes swelling of the face or throat (angioedema), anaphylactoid/anaphylactic reactions (serious allergic reaction which causes difficulty in breathing or dizziness), glucose intolerance, depression, mood disturbances, irritability, exacerbation of chorea (St. Vitus's dance), exacerbation of epilepsy, dementia, exacerbation of asthma, yellowing of the skin (jaundice), inflammation of the pancreas, benign neoplasm of the smooth muscle of the womb, discolouration of the skin especially of the face or neck known as "pregnancy patches" (chloasma or melasma) - that may persist when drug is discontinued; painful reddish skin nodules (erythema nodosum); rash with target-shaped reddening or sores (erythema multiforme), haemorrhagic eruption, loss of hair, pain in a joint, secretion of milk from the breast, lumpiness in the breasts, increase in size of benign neoplasm of the smooth muscle of the womb, changes in the secretion and the inner lining of the cervix ("neck" of the womb), inflammation of the vagina, fungal infections in the vagina (vaginal candidiasis), abnormally low level of calcium in the blood.

How to store Lenzetto?

Do not refrigerate or freeze this medicine. Do not store above 25°C.

Use within 56 days of first use.

It contains ethanol which is flammable. Store away from heaters or naked flames.

Keep this medicine out of the sight and reach of children.

Scientific discussion

during the initial phase

This module reflects the scientific discussion for the approval of Lenzetto 1.53 mg/spray transdermal spray, solution. The procedure was finalised at 25 June 2015. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

In accordance to the Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 *on the Community code relating to medicinal products for human use*, an application has been submitted to the reference and competent authorities of the Member State concerned.

This Decentralised Procedure application (Reference member state, RMS: Hungary, concerned member states, CMS: Austria, Belgium, Bulgaria, Croatia, Cyprus, the Czech Republic, Denmark, Estonia, Finland, Germany, Greece, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Romania, the Slovak Republic, Slovenia, Spain, Sweden and the United Kingdom) concerned a transdermal spray of estradiole (in estradiole hemihydrate form).

The application has been filed pursuant to Article 8 (3) of Directive 2001/83/EC (full application).

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorization for Lenzetto 1.53 mg/spray transdermal spray, solution containing estradiol hemihydrate, Gedeon Richter Plc., Hungary.

The marketing authorisation has been granted pursuant to Article 8.3 of Directive 2001/83/EC as a mixed application of a known active substance. The applicant has followed the recommendations laid in the *Guideline on clinical investigation of medicinal products for hormone replacement therapy of estrogen deficiency symptoms in postmenopausal women* EMEA/CHMP/021/97 Rev. 1.

No Pediatric Investigation Plan has been submitted as the proposed indication falls under the scope of the Agency Decision CW/1/2011 "*Treatment of climacteric symptoms associated with decreased estrogen level, as occurring at menopause*". Therefore, the class waiver is acceptable.

The product is indicated as Hormone replacement therapy (HRT) for estrogen deficiency symptoms in postmenopausal (natural or surgical menopause, with or without a uterus) women. Lenzetto is to be applied once daily to the forearm as a starting dose and may be increased to two or three sprays daily to the forearm based on clinical response. When estrogen is prescribed for a postmenopausal woman with a uterus, a progestagen approved for addition to estrogen treatment should also be initiated to reduce the risk of endometrial cancer. The current recommendation by the EMA Committee for Medicinal Products for Human Use (CHMP) (EMEA/CHMP/021/97) and the US Food and Drug Administration (US FDA Guidance for Industry (draft) 2003) is to use the lowest available and approved dose of estrogen, for the shortest period of time, to treat vasomotor symptoms (VMS).

A comprehensive description of the indications and posology is given in the Summary of Product Characteristics (SmPC).

Estradiol is the most potent of the naturally occurring estrogens. It promotes the growth and maintenance of the female reproductive tract and secondary sexual characteristics. The decline in ovarian estrogen production at the menopause leads to vaginal atrophy and, in many women, vasomotor symptoms ('hot flushes'). Postmenopausal vascular symptoms can be reversed by treatment with estrogens such as estradiol.

Lenzetto is a novel transdermal estradiol replacement product that delivers therapeutic doses of estradiol to the skin, using a metering pump containing 1.53 mg/dose estradiol hemihydrate as active substance and 85mg/ml octisalate (ethylhexyl salicylate) as a skin penetration enhancer excipient in ethanol 95%. Transdermal delivery of estrogen is well established in clinical practice and can lead to sufficient serum estradiol levels to alleviate (VMS) at lower overall estradiol exposure while avoiding some of the consequences of high hepatic exposure and first-pass metabolism. Daily sprays create a depot within the skin, from which estradiol is continuously absorbed into the circulation throughout the 24 hour dosing cycle. Octisalate, a common ingredient of sunscreen, is used in the Estradiol 1.53 mg/spray MDTS formulation as a skin penetration enhancer.

II. QUALITY ASPECTS

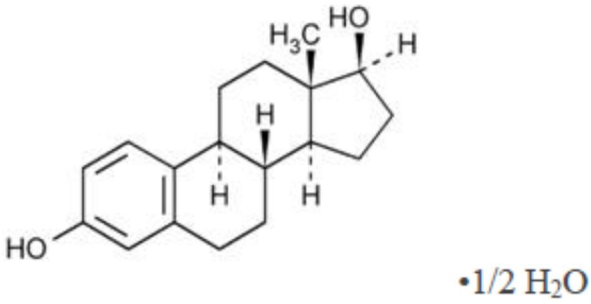
II.1 Introduction

The chemical-pharmaceutical assessment report concerns the application of Lenzetto 1.53 mg/spray transdermal spray, solution via a decentralized procedure according to Article 8(3) of Directive 2001/83/EC (i.e. dossier with administrative, quality, pre-clinical and clinical data).

II.2 Drug substance

Data on the quality and manufacture of the active substance were provided in the submission using the European Pharmacopoeia (Ph. Eur.) Certificate of Suitability (CEP) procedure with additional data in the marketing authorization dossier. The Quality Overall Summary is adequate.

INN name: estradiol
Chemical name: estra-1,3,5(10)-triene-3, 17β –diol hemihydrate
Structure:



The active substance is white or almost white crystalline powder or colourless crystals practically insoluble in water, soluble in acetone, sparingly soluble in ethanol (96 per cent), slightly soluble in methylene chloride.

The substance is specified according to the requirements of the current Ph. Eur. monograph. Additional specification has only been set for residual solvents and microbiological quality.

The Ph. Eur. specification includes the following tests for estradiol hemihydrate: characters, specific optical rotation, identification, test for purity, water content and assay.

Testing methods not described in details in the Pharmacopoeia are adequately drawn up and sufficiently validated. Reference materials used by the active substance manufacturer and the drug product manufacturer for the control of the substance are adequately characterised.

The substance complies with the requirements of the European Medicines Agency (EMA) guideline on genotoxic impurities.

Batch analysis data justify the limits, indicate the good performance of testing methods and demonstrate the batch to batch consistency of the production.

A retest period and the packaging material (double polyethylene bag placed in fiber drum) have been mentioned on the CEPs.

Good Manufacturing Practice (GMP) compliance of the API manufacture is demonstrated by the applicant.

II.3 Medicinal product

The aim of the development was to develop a manual pump, metered-dose product containing estradiol as active substance, using octisalate in ethanol solution.

A satisfactory package of data on development pharmaceutics has been presented. Brief discussion on reasons for inclusion and quantity of excipients has been provided.

The compositions and the pharmaceutical tests evaluated during development of the final formulation are included in the documentation. As a result of development studies product with the following appearance, composition and packaging was obtained.

Each spray delivers 90 microliter of clear, colourless to pale yellow transdermal spray, solution containing 1.53 mg of estradiol (equivalent to 1.58 mg of estradiol hemihydrate). The solution is packaged in a glass vial fitted with a metered dose pump encased in a plastic housing with a conical bell opening.

The excipients used in the finished product are octisalate and ethanol 96%. Ethanol complies with respective European Pharmacopoeia monograph. Octisalate complies with respective USP monograph.

A description and flow chart of the manufacturing method have been provided. Appropriate in-process controls are included in the manufacturing process. Satisfactory batch formulae were also presented. GMP compliance of the manufacturing site has been demonstrated.

The finished product specification is satisfactory. Acceptance criteria have been justified with respect to conventional pharmaceutical requirements as prescribed in the relevant dosage form monograph of the Ph. Eur. and the International Conference on Harmonisation (ICH) Q6A guideline. Appropriate control strategy was selected. The test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and complied with the specification.

The container closure system of the product is a glass vial fitted with a metered dose pump which in encased in a plastic housing with a conical bell opening. Specifications and quality certificates for all packaging components are enclosed.

Finished product stability studies have been conducted in accordance with the current guidelines. Based on the results, a shelf-life of 3 years with "Do not store above 25°C" and "Do not refrigerate or freeze" storage conditions is approved.

The SmPC, Patient Information Leaflet (package leaflet) and label texts are pharmaceutically acceptable.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The product has been shown to meet the current regulatory requirements with regards to its quality and content of the active substance as well as dosage-form characteristics until the end of the approved shelf-life consistently. The manufacture and the quality standards applied adequately support the safe use and efficacy of the product.

From chemical-pharmaceutical points of view the product is approvable.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of both the active substance estradiol and the excipient octisalate are well known. Claiming that both drugs are widely used and well-known the applicant has not performed further studies. The overview is based on literature data.

In case of an Article 8(3) (of Directive 2001/83/EC), mixed application this solution is acceptable.

III.2 Pharmacology

In line to what was said in the introduction, no new pharmacology studies have been performed in support of this application. The applicant has provided an overview of all non-clinical pharmacology data available in the published literature for both estradiol and octisalate. Estradiol has a well-established use and an extensive knowledge of its pharmacology is available in the treatment of post-menopausal symptoms. Moreover, a variety of oral and transdermal products is available. Octisalate has been in widespread use as an ingredient of over-the-counter sunscreen and cosmetic products for many years.

Thus, the lack of new non- clinical pharmacology data is accepted.

III.3 Pharmacokinetics

No new pharmacokinetic studies have been submitted in support of this application. The applicant pointed out that the pharmacokinetics of estradiol is extensively characterized, the absorption of topically-applied octisalate is limited with recovery of low amounts mostly in the epidermis, and complete absorption is likely to be less than 1%. It can be endorsed.

Transdermal delivery of estradiol avoids the extensive metabolism that occurs with oral administration and is well established in clinical practice. Estradiol is absorbed through the skin and the contemporary use of a penetration enhancer encourages the development of a local depot assuring an even and continuous low level of exposure. Estradiol is widely distributed in the tissues with similar levels in a variety of organs being higher than those found in plasma. The metabolism of estradiol is complicated and species specific with no animal model fully reproducing the human metabolism. Excretion, in women, is primarily as estrone in the urine and as conjugates in the bile and urine. A variety of other metabolites are excreted in animal species.

In vitro and *in vivo* (clinical) skin permeation studies with octisalate (ethylhexyl salicylate) demonstrate limited absorption into the stratum corneum and very little penetration into the

deeper layers of the skin. The high lipophilicity of octisalate makes the partitioning step from the lipophilic environment of the stratum corneum into the underlying, progressively more aqueous, layers of the skin, unfavorable. It can therefore be concluded that the systemic absorption of octisalate is limited (likely to be less than 1%).

III.4 Toxicology

No studies were performed concerning toxicity of estradiol by repeated administration, the effects on reproductive functions, the genotoxic and carcinogenic potential. The expert discussed data from literature, which are numerous but part of them are old and do not meet the present quality requirements. Estradiol induces toxicological effects on the hematopoietic, reproductive and endocrine systems and the skin. Genotoxic and carcinogenic effects of estradiol have been reported in the literature.

When considering the long clinical experience with topical administration of estradiol, resulting in systemic exposures at or above those achieved with Lenzetto, there are no concerns for human safety at the proposed clinical use.

Reproduction studies in rats and mice show that estradiol at high doses inhibits pregnancy, consistent with the contraceptive effect in humans. Estradiol exposure during early gestation causes embryotoxicity, and significant effects on the development of the reproductive system are apparent at estradiol exposures during gestation only a little higher than the normal physiological levels. Since the proposed indication for Lenzetto is use in postmenopausal women, there are no concerns for human safety.

The toxicology package presented for octisalate is considered limited, with deficiencies in the documentation on repeat dose toxicity and genotoxicity. There are however other documentation available that has been assessed. It indicates that the both the acute oral toxicity of octisalate and that the sub-chronic toxicity following dermal or oral route of administration is 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. This information has been published by the Scientific Committee on Cosmetic and non-food products (SCCNFP) which is the advisory body to the European Commission in matters of consumer protection with respect to cosmetics and non-food products. No animal studies of potential carcinogenesis associated with octisalate treatment have been identified. To conclude, the toxicology profile of octisalate is found to be safe at a concentration of 5% as when used in cosmetics. The percentual concentration of octisalate in Lenzetto is 8.5 percent as opposed to the 5% that is set as limit by the European cosmetic legislation. The applicant argues that a person would only need to use sunscreen on 6-7 occasions a year, to have the same total exposure to octisalate as a daily dose of 3 sprays of Lenzetto for a year is endorsed.

No animal studies on effects of octisalate on reproductive or developmental toxicity have been performed but this can be accepted considering the limited systemic absorption of octisalate.

Local tolerance to Lenzetto: no non-clinical local tolerance studies have been performed with the formulation proposed for marketing. Considering the nature of the product (a simple ethanol solution with estradiol and octisalate) and that clinical safety data is available, the absence of local tolerance studies with the final formulation is considered justified.

III.5 Ecotoxicology/environmental risk assessment (ERA)

In agreement with the relevant ERA guideline that requires that "certain substances, such as highly lipophilic compounds and potential endocrine disruptors, may need to be addressed irrespective of the quantity released into the environment" the applicant has submitted an Environmental Risk Assessment supplemented with a Fish Full Life Cycle Test. Since ecological effects of estradiol and its metabolites have been extensively studied the results communicated in the report are literature based. The outcome of the reported Fish Full Life Cycle Test confirms the known environmental impact of estradiol. The applicant's argumentation, that the repetition of the test would be unnecessary as it would not result in additional information regarding the effects of estradiol on the fish reproduction and development is accepted.

Also the argumentation that – as 17β-estradiol is intended to be used as a substitute for other identical products on the market, the use of Lenzetto 1.53 mg/spray transdermal spray will not result in an increase in the total quantity of endocrine disruptors released into the environment, moreover, the product Lenzetto 1.53 mg/spray transdermal spray containing 17β-estradiol does not contain any component which results in an additional hazard to the environment – can be accepted.

Instructions for handling of product waste are properly emphasized in the product information.

III.6 Discussion on the non-clinical aspects

Taking into account that estradiol has a well-established use and an extensive knowledge on pharmacology, pharmacokinetics and toxicology data, octisalate has been in widespread use as an ingredient of over-the-counter sunscreen and cosmetic products for many years, the absorption of topically-applied octisalate is very limited, the lack of own, new nonclinical data can be accepted.

The non-clinical part of the application is acceptable.

IV. CLINICAL ASPECTS

IV.1 Introduction

Transdermal delivery of estradiol provides estrogen replacement therapy while avoiding some of the consequences of high hepatic exposure and first-pass metabolism. Lenzetto 1.53 mg/spray transdermal spray is dissimilar to existing transdermal systems in that the estradiol is not formulated as a membrane controlled reservoir or solid matrix system requiring a backing, release liner and adhesive. Accordingly, Lenzetto 1.53 mg/spray transdermal spray has several potential advantages over currently approved transdermal estrogen products. The estradiol transdermal spray goes on clear, dries in less than two minutes and has a low incidence of reported skin irritation. Clinical studies have shown that the estradiol delivered in the Lenzetto 1.53 mg/spray transdermal spray formulation is absorbed through the skin and provides efficacious serum concentrations for the treatment of VMS in postmenopausal women. The fast-drying spray delivers a low dose of estradiol, resulting in therapeutic blood levels similar to the low end of the exposure range for other approved estrogen products.

In the phase of formulation development five phase 1 clinical studies have been performed using various proportions of estradiol and two different penetration enhancers in order to identify an appropriate formulation that would result in therapeutic levels of systemic estradiol when delivered via a transdermal spray.

Also three sponsored clinical studies have been performed with Lenzetto 1.53 mg/spray transdermal spray: a phase 3 safety and efficacy; a study on pharmacokinetics; and a study to evaluate factors that could affect estradiol absorption.

IV.2 Pharmacokinetics

In vitro and *in vivo* (clinical) skin permeation studies with octisalate demonstrate limited absorption into the stratum corneum and very little penetration into the deeper layers of the skin. The high lipophilicity of octisalate makes the partitioning step from the lipophilic environment of the stratum corneum into the underlying, progressively more aqueous, layers of the skin, unfavorable. It can therefore be concluded that the systemic absorption of octisalate is limited.

The distribution, metabolism and excretion of estradiol described in the package labeling for approved estrogen replacement products are indicative of the drug class and are similar among products and therefore, specific studies describing the distribution, metabolism or excretion of estradiol absorbed from Lenzetto have not been conducted.

Systemic estrogen replacement therapy can be administered orally or transdermally. The disadvantage of oral estrogen replacement therapy is that high doses must be administered to compensate for extensive first-pass metabolism.

Early development work on the estradiol spray formulation involved varying the types and concentrations of penetration enhancer, the concentration of estradiol, and the volume of spray applied to the skin. The formulation containing 1.7% estradiol and 8.5% octisalate was ultimately selected for subsequent clinical studies. Due to a change in the pump selected for the final commercial product, the dosing volume was adjusted to 90 µl.

The pharmacokinetic studies have characterized the pharmacokinetic properties of Lenzetto and factors influencing the absorption from the new dosage form have also been evaluated.

The pharmacokinetic study investigated the steady-state pharmacokinetics of three different doses of estradiol transdermal spray applied to the forearm of postmenopausal women.

A separate study assessed the influence of various factors on the absorption of estradiol from the spray, i.e. possible transfer to another individual, influence of washing the application site and effect of sunscreen use at the application site.

Summary of results:

- Mean concentrations of all three analytes (estradiol, estrone and estrone sulfate) appeared to reach steady state by Day 7 or Day 8, but did not return to the baseline by 1 week after the end of dosing.
- Mean serum concentrations of estradiol, estrone and estrone sulfate from 1, 2, or 3 sprays of estradiol transdermal spray increased with dose.
- Based on the day 14 data, geometric means baseline-adjusted estradiol C_{avg} values were 13.5, 24.3, and 25.9 pg/ml for the 1-, 2- and 3-spray groups, respectively.
- Dose proportionality for estradiol as administered in this study was inconclusive for AUC_{0-24} on day 14 due primarily to the small differences in these values between the 2- ad 3-spray doses. Although there appeared to be a separation of dose groups on day 1-13, there was insufficient data to draw firm conclusion regarding dose proportionality during this phase of the study. Based on pre-dose serum estradiol levels on days 2-13, there was an appreciable increase in exposure with increasing dose; however the pharmacokinetic results on day 14 showed considerable overlap between 2 and 3-spray dose levels. Thus, firm conclusion regarding dose proportionality could not be drawn.
- Median values for T_{max}, the time to the maximum estradiol concentration, occurred at 18 to 20 hours after dosing.
- Pharmakokinetic values for C_{max}, T_{max} and C_{avg} using the proposed formulation were similar to those in a previous study that involved comparable doses with the same formulation.
- Estradiol metered dose transdermal spray (MDTS) was well tolerated. No skin reactions were observed at the application site.
- Skin-to-Skin Transfer: based on an equivalence analysis using $AUC_{(0-24)}$, no significant transfer of estradiol was observed in persons (males) who came in direct contact with the application site of the estradiol-treated individuals (females).
- Washing Effect: based on an equivalence analysis using $AUC_{(0-24)}$, washing the site of application 1 hour after study drug application did not have a significant effect on the systemic exposure of estradiol delivered topically using estradiol MDTS.
- Sunscreen Use: there was a decrease in the systemic exposure of estradiol when sunscreen was applied 1 hour post study drug application compared to the control estradiol period (9% decrease in exposure for baseline-adjusted and 11% decrease in baseline-unadjusted

data). No difference from the control estradiol period was observed in the systemic exposure of estradiol when sunscreen was applied 1 hour prior to study drug application. Baseline-adjusted and baseline-unadjusted concentrations resulted in similar trends.

- Drying Time for estradiol MDTS: overall mean and median drying times for the three sprays in each dose were 84.9 and 67 seconds, respectively. Overall drying times ranged from 30 to 242 seconds (4 minutes). The reason for this considerable variability is not known.
- Estradiol MDTS was well tolerated. The number of adverse events was low and all were mild.

Based on the systemic exposure data, the doses of Lenzetto 1.53 mg/spray transdermal spray being sought for approval are within the range of other approved drugs of this type currently marketed globally.

In the pharmacokinetic study the estradiol levels appeared to increase in a relatively proportional manner to the number of sprays administered up to day 14, however, on day 14, there was sudden increase in mean estradiol concentrations in the group receiving 2 sprays, and thus, dose proportionality could not be concluded exactly.

When the 24-hour concentration vs. time profiles for Lenzetto were assessed, it was shown that when doses of Lenzetto were applied in the morning (8:00 a.m.) there was an apparent peak in serum estradiol levels during early morning hours of the following day. This was observed at all dose levels, and also in other studies where 24-hour levels were monitored. The cause of this early morning spike has not been confirmed.

The effect of washing and sunscreen use was studied after single dosing on three different occasions (days 11, 14 and 17). Thus, a new steady state was not reached with each of these different factors studied. Washing the application site with soap and warm water one hour after applying the estradiol transdermal spray did not seem to affect estradiol absorption. However, since the application site was the same at all study days, a skin depot of estradiol may be present and the observed effect of washing on a single application occasion may have been underestimated. No analysis of the amount of estradiol recovered in the washing water seems to have been performed. The information provided in the SmPC and PL concerning washing of the application site is acceptable.

Sunscreen administration one hour prior to study drug application did not affect the absorption of estradiol compared to the control, whereas a 10% decrease in estradiol exposure occurred when sunscreen was applied one hour after the estradiol transdermal spray relative to the control period. As for the washing effect, the study design may have an impact on the results, since the sunscreen tests were performed at steady state and a new steady state was not reached with the new administration condition. The effect is most probably clinically not relevant.

A dedicated clinical study was conducted and submitted by the company to compare the rate and extent of absorption of Estradiol MDTS 1.53 mg/dose (90 µl) at normal versus high ambient temperature, in 24 healthy post-menopausal females, after administration of 2 sprays on the forearm. The applicant concludes that according to the own data and published scientific

literature the increased body temperature does not lead to significant differences in plasma levels of estradiol, which would suggest clinically relevant differences in efficacy or safety of estradiol metered-dose transdermal spray.

According to literature data body weight and BMI may have a significant effect on the rate and extent of absorption of a transdermal drug product. To evaluate the influence of obesity on the absorption, the applicant conducted a single-dose, comparative BA study concluding that 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 when estradiol MDTS 1.53 mg/spray (90 µl) under normal temperature conditions was administered in obese post-menopausal females compared to normal weight post-menopausal females.. These findings have been included in SmPC section 5.2 and also a note on possible need for dose adjustment in obese women in section 4.2. Based on the data described above, these texts are considered acceptable.

The influence of different application sites has not been assessed with the final commercial formulation of Lenzetto, however, data are available from earlier studies. Based on one study, it was concluded by the applicant that application of estradiol transdermal spray to the abdomen seemed to result in lower systemic concentrations of estradiol than application of comparable doses to the forearm. This may partly have been influenced by the treatment period of only 5 days and steady state may not have been reached. In another study it was shown that administration on the inner thigh seems to result in somewhat higher estradiol concentrations compared with administration on the forearm. In the SmPC application of the spray on the forearm is recommended, with the inner thigh as a possible alternative, whereas administration on the abdomen is not recommended. Based on the data described above, these recommendations are considered acceptable.

IV.3 Pharmacodynamics

No new pharmacodynamic studies were performed by the applicant.

Estradiol transdermal spray pharmacokinetic parameters are at or below the range produced by other transdermal estradiol products with nominal estradiol delivery rates of 50 µg/day and are expected to be effective in reducing climacteric symptoms in post-menopausal women and remain in a safe dose range, thus the lack of pharmacodynamic studies is endorsed.

IV.4 Clinical efficacy

The pivotal efficacy data for estradiol 1.53 mg/spray transdermal spray comes from a single, double-blind, placebo controlled, multi-center, Phase 3 study with six parallel arms (3 treatment, 3 placebo). Its objectives were to evaluate the safety and efficacy of estradiol transdermal spray in the treatment of vasomotor symptoms. Safety, adverse events, skin tolerability, biopsy proven endometrial status, spontaneous vaginal bleeding, cervical smears, clinical laboratory values and physical examinations. The subject population was: postmenopausal women with a mean frequency of 56 or more moderate to severe hot flushes per week

Summary of results: the primary endpoints evaluated the frequency and severity of moderate to severe hot flushes at week 4 and week 12 of treatment for each of the 3 dose levels. The results confirm, in all 3 groups, that the active treatments were effective in relieving typical estrogen deficiency symptoms.

The supplemental diary endpoints showed a significant difference between estradiol and placebo in the change in frequency and severity of moderate to severe vasomotor symptoms by week 2 in all dose groups.

In the responder analysis with the lowest dose studied, 43 % of the estrogen-treated women experienced a 90% reduction of the frequencies of hot flushes. The treatment had a weaker effect on the severity of the vasomotor symptoms with 25% experiencing a 90% reduction of the vasomotor symptoms with the lowest dose.

The results confirm that active treatments were effective in relieving typical estrogen deficiency symptoms with no difference between the different dose groups.

Improvement was found in Greene Climacteric scale and Global Assessment and confirm that active treatments were effective in relieving typical estrogen deficiency symptoms with no difference between the different dose groups.

The results concerning secondary endpoints showed significant effects on the frequency and severity of moderate and severe hot flushes at week 8.

The results confirm, in all 3 groups, that the active treatments were effective in relieving typical estrogen deficiency symptoms. Although no clear dose-response relationship between the 1- 2- and 3-spray doses was observed in the primary efficacy variable, higher exposure of estradiol correlates with greater improvement in frequency and severity of moderate and severe hot flushes. A starting dose of 1 spray/day is proposed in the SmPC, and it is described how titration to a higher dose should proceed.

In accordance with the *Guideline on clinical investigation of medicinal products for hormone replacement therapy of estrogen deficiency symptoms in postmenopausal women*. EMEA/CHMP/021/97 Rev. 1.for the evaluation of such products, treatment of vasomotor symptoms in menopausal women should start at the lowest possible dose required to achieve clinical efficacy. The exposure levels seen in this study are comparable to or less than the exposure associated with other estradiol products approved for the treatment of vasomotor symptoms. Nonetheless, the 1-spray dose of Lenzetto provides symptom relief, as evidenced by clinically and statistically significant reductions in frequency and severity of moderate and severe hot flushes. The borderline statistical significance seen in the severity score (SS2) at week 4 provides some evidence that the 1-spray dose may represent the lowest effective dose of transdermal estradiol for the treatment of vasomotor symptoms.

Correlation data were confirmed by a post-hoc analysis that compared serum estradiol levels in subjects who achieved a 75% reduction in frequency of moderate to severe vasomotor

symptoms (responders) to serum levels in subjects who did not (non-responders). The mean (geometric) estradiol concentration among subjects who were responders was 27.7 pg/ml (95% CI 23.1-33.2 pg/ml) compared to 19.4 pg/ml (15.5-24.4 pg/ml) measured in the non-responders.

Both the regression analysis of estradiol exposure and vasomotor symptom frequency, and the 75% responder analysis, indicate that there is an exposure-response relationship that exists for estradiol transdermal spray within the dose range studied. Thus, higher estradiol exposures are associated with greater reductions in the frequency of vasomotor symptoms.

With respect to dosing of Lenzetto, these results suggest that, for individuals not achieving an acceptable level of vasomotor symptom relief at the starting dose, a higher dose of estradiol may provide an improved reduction in vasomotor symptom frequency or severity. The suggested use of this product will be to up-titrate as indicated by clinical response in single spray dose increments, up to a total of 3 sprays if so required. Titration should be performed solely on the basis of clinical response, and no blood level monitoring is indicated. Subpopulation analyses done during the Phase 3 study show no apparent differences based on age, BMI, race, or menopausal status, and no specific dosing or titration recommendations apply for these subpopulations.

IV.5 Clinical safety

The submitted documentation evaluates safety data of the participating subjects exposed to estradiol transdermal spray in all 3 clinical studies.

In women with a uterus, a combination with a progestogen is necessary to avoid endometrial hyperplasia. Since no study on endometrial safety has been performed on the actual dose in combination with a progestogen, conclusions have to be made from the 12 week study of unopposed Lenzetto treatment.

Subjects with an intact uterus were required per protocol to take medroxyprogesterone acetate (MPA) 5mg or 10 mg per day for 2 weeks following the completion of treatment to mitigate any possible increased risk of endometrial hyperplasia resulting from unopposed estrogen therapy. The safety population was hysterectomized in 56%.

The application fulfills the minimum criteria for treatment of estrogen deficiency symptoms according to the *Guideline on clinical investigation of medicinal products for hormone replacement therapy of estrogen deficiency symptoms in postmenopausal women*. EMEA/CHMP/021/97 Rev. 1.

The safety data from the phase 1 and 3 studies did not show any adverse events that are unexpected for an estradiol product.

With regard to the endometrial bleeding pattern, bleeding disturbances were more related to Lenzetto treatment than placebo. The endometrial data suggest a low risk of endometrial hyperplasia after 12 weeks of Lenzetto treatment, although the results are limited. In clinical

treatment, the estrogen should be combined with a progestogen in women with a uterus, to prevent endometrial hyperplasia.

No long term safety study supporting endometrial safety was conducted by the applicant. According to the *Explanatory note on HRT* (CPMP/EWP/021/97), when bioavailable doses do not exceed those of approved marketed products, specific studies calling for endometrial biopsies are not required: "for a new medicinal product containing as active substance an estrogen which would show an increase in bioavailability compared to a reference product, endometrial data may be required."

Although no comparative pharmacokinetic studies vs. known and widely used reference products were conducted with the final formulation to confirm that Lenzetto delivers estradiol doses within the intervals for which endometrial safety is considered established the applicant has provided a comprehensive evaluation of estradiol exposure following 1, 2 and 3 sprays of Estradiol MDTS relative to other marketed transdermal products to evaluate if the Lenzetto product shows increased (or decreased) bioavailability. Data suggests that Lenzetto used at its highest dose is unlikely to exceed the estradiol systemic exposure when compared with other marketed products.

The applicant submitted an analysis on the post-marketing safety data of the product marketed in the USA since 2008 as requested. The estimated patient exposure was very high. Among the adverse events reported in connection with estradiol containing transdermal products marketed in the USA. Among the adverse events reported only about 1.5% was serious and no individual case safety reports (ICRS) were received regarding the topic of endometrial hyperplasia during the period of this report. There is no evidence to suggest an increased risk of long-term application site reactions either with Lenzetto.

The product labelling provides clear instructions for safe and effective use of the product.

Taking into consideration that doses of Lenzetto were associated with comparable levels of estradiol exposure to other products approved for HRT, that no ICSR was received concerning the topic of endometrial hyperplasia there is no evidence to suggest an increased risk of long term safety problems, thus the lack of a long term safety study can be accepted.

IV.6 Pharmacovigilance

IV.6.1 Summary of the Pharmacovigilance Plan

The applicant has submitted a signed Summary of the Applicant's Pharmacovigilance System. Provided that the Pharmacovigilance System Master File fully complies with the new legal requirements as set out in the Commission Implementing Regulation 520/2012 and as detailed in the relevant Good Vigilance Practice module, the Summary is considered acceptable.

IV.6.2 Risk Management Plan

Summary of safety concerns	
Important identified risks	Venous and arterial thromboembolic events (including deep vein thrombosis, pulmonary embolism, Ischaemic stroke and coronary artery disease). Endometrial hyperplasia / Endometrial cancer Breast cancer. Ovarian cancer. Unintentional Secondary Exposure.
Important potential risks	Medication error (Overdose). Hypersensitivity to octisalate.
Missing information	Application site reactions. Long term use.

Routine pharmacovigilance activities are considered sufficient to manage all of the safety concerns connected to Gedeon Richter Plc.'s product Lenzetto 1.53 mg/spray transdermal spray solution. No additional activities are proposed and are necessary.

Routine risk minimisation measures (i.e. wording in SmPC, package leaflet and clasification as a prescription-only medicine) are considered sufficient to manage all of the safety concerns connected to Lenzetto 1.53 mg/spray transdermal spray solution. No additional activities are proposed and are necessary.

IV.6.3 Periodic Safety Update Reports

Periodic Safety Update Reports (PSURs) shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the Data Lock Point (DLP) and frequency of submission of the next PSUR.

According to the latest EURD list (16 June 2015, EMA/630645/2012 Rev.31) PSUR for estradiol containing products should be submitted 5-yearly, the next DLP will be 31. 08. 2016. Since the legal basis of the application is Article 8(3) (mixed) with known active substance, the applicant has to submit PSURs.

IV.7 Discussion on the clinical aspects

The application concerns an Article 8.3 (mixed) application of known active substance. The indication is hormone replacement therapy (HRT) for estrogen deficiency symptoms in post-menopausal (natural or surgical menopause, with or without a uterus) women.

The applicant has provided literature data and data from three sponsored clinical studies: a phase 3 safety and efficacy; a study on pharmacokinetics; and a study to evaluate factors that could affect estradiol absorption. These studies showed that, in all 3 doses treatments were effective in relieving typical estrogen deficiency symptoms. Although no clear dose-response relationship between the 1- 2- and 3-spray doses was observed in the primary efficacy variable, higher exposure of estradiol correlates with greater improvement in frequency and severity of moderate and severe hot flushes.

The safety data from the phase 1 and 3 studies with Lenzetto did not show any adverse events that are unexpected for a transdermal estradiol product. Taking into consideration that doses of estradiol MDTS were associated with comparable levels of estradiol exposure to other products approved for HRT, that no ICSR was received concerning the topic of endometrial hyperplasia there is no evidence to suggest an increased risk of long term safety problems, thus the lack of a long term safety study can be accepted.

There is no objection against granting the marketing authorization from a clinical point of view.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

V.1 Summary

The application concerns Lenzetto 1.53 mg/spray spray transdermal solution. The active substance of the product is estradiol. The applicant and the future holder of authorisation is Gedeon Richter Plc.

This is an Article 8.3 (mixed) application of known active substance. The indication is hormone replacement therapy (HRT) for estrogen deficiency symptoms in postmenopausal (natural or surgical menopause, with or without a uterus) women.

The applicant has provided non-clinical and clinical literature data as well as data from three sponsored clinical studies: a phase 3 safety and efficacy; a study on pharmacokinetics; and a study to evaluate factors that could affect estradiol absorption. These studies showed that the treatments were effective in relieving typical estrogen deficiency symptoms.

The submitted documentation is administratively adequate and scientifically sound. The quality of the product is satisfactory. There were no non-clinical or clinical concerns raised.

The therapeutic benefit/risk assessment is, therefore, positive.

Based on the review of the quality, safety and efficacy data, the Member States have granted marketing authorisation for Lenzetto 1.53 mg/spray spray, transdermal solution.

V.2 Classification

Prescription-only medicine.

V.3 Package Leaflet and user consultation

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the patient information leaflet was Hungarian.

The results show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

VI. Upgrade: steps taken after the initial procedure with an influence on the Public Assessment Report

This module reflects the procedural steps and scientific information after the finalisation of the initial procedure.

Scope	Procedure number	Product information affected	Date of start of the procedure	Date of end of procedure	Approval or non approval	Assessment report attached