

| Safety concern | Routine risk minimisation measures   | Additional risk minimisation measures |
|----------------|--|---------------------------------------|
|                | <p>connection with long term use.</p> <p><i>Section 5.3</i> revealed increased frequency of carcinoma of the breast, uterus, cervix, vagina, testes and liver in certain animal species during long term continuous administration of natural and synthetic estrogens.</p> <p>Prescription only medicine</p> |                                       |

## VI.2 Elements for a Public Summary

### VI.2.1 Overview of disease epidemiology

About 75% of women experience vasomotor symptoms (VMS) like flushes and sweating around menopause. Many women also report depressed mood, sleep disturbances and other psychological problems, which may affect quality of life and be attributed to exogenous factors, but also to hormonal changes related to menopause.

### VI.2.2 Summary of treatment benefits

The benefits of estradiol for the treatment of vasomotor symptoms associated with the menopause are well understood, and estrogen products have been used for nearly half a century to alleviate these symptoms. To date, no other class of drugs has been shown to be more effective for the treatment of vasomotor symptoms (i.e. hot flushes).

In a pivotal study of 454 women, treatment with one, two or three sprays provided efficacy responses comparable to those seen with other transdermal estradiol products. The lowest effective dose was identified by this study as one spray per day, which delivered a dose of approximately 1.53 mg/spray. If needed, the dose can be titrated to two or three sprays per day to increase the systemic exposure and corresponding amelioration of symptoms. Among the various transdermal estradiol products that are currently available, there is a relatively wide range of available doses and resulting levels of exposure to estradiol. The side effect profile due to systemic estradiol exposure was also comparable to other products (see detailed information in section VI.2.4 Summary of safety concerns) and no new safety concerns were identified.

### VI.2.3 Unknowns relating to treatment benefits

Not applicable.

### VI.2.4 Summary of safety concerns

#### Important identified risks

| Risk   | What is known   | Preventability   |
|--|---|--|
| <p><b>Blood clots in vessels (venous and arterial thromboembolic diseases: in the legs, in the lungs, in the brain, in the heart or in other organs)</b></p> <p>(Venous and arterial thromboembolic events (including deep vein thrombosis, pulmonary embolism, Ischaemic stroke and coronary artery disease))</p> | <p><i>{Invented name}</i> is a hormone replacement therapy (HRT). It is used in postmenopausal women with at least 6 months since their last natural period. <i>{Invented name}</i> can also be used in woman who have had surgery to remove their ovaries as this causes instant menopause. It contains the female hormone, oestrogen. Using a HRT, like <i>{Invented name}</i> bears a higher risk of developing a vascular occlusion of the veins caused by a venous blood clot (thromboembolism) compared to patients who do not use such therapies. The risk of blood clots in the veins is about 1.3 to 3-times higher in HRT users than in non-users, especially during the first year of using it.</p> <p>Blood clots can be serious, and if one travels to the lungs, it can cause chest pain, which can spread to arm and neck, breathlessness, painful swelling and redness in the legs, changes in speech, changes in vision, fainting or even death.</p> <p>The risk of blood clots in users of HRT increases:</p> <ul style="list-style-type: none"> <li>• with increasing age</li> <li>• in seriously overweight patients (BMI &gt;30 kg/m<sup>2</sup>)</li> <li>• if the woman is unable to walk for a long time because of major surgery, serious injury or accident, or if she is immobilized for a long time due to other serious illnesses</li> <li>• if the patient previously had blood clots in her leg, lung or in other organs or if the woman have any blood clotting problem that needs</li> </ul> | <p><i>{Invented name}</i> should be used only after consultation with a doctor and regular check-ups are needed.</p> <p>The following healthy lifestyle can help to prevent blood clots: regular physical activity, avoiding smoking, maintaining healthy weight, controlling blood sugar, blood pressure and cholesterol levels.</p> <p>As a precaution measure, hormone replacement therapies should not be used</p> <ul style="list-style-type: none"> <li>• if the patient has or has ever had a blood clot in her veins. This may cause blockage of a blood vessel in the legs (deep vein thrombosis) or in her lungs (pulmonary embolism) or other organs;</li> <li>• if the patient has a blood clotting disorder (such as protein C, protein S or antithrombin deficiency);</li> <li>• if the patient has, or recently have had a disease caused by blood clots in the arteries, such as heart attack, stroke or severe chest pain due to angina (angina pectoris)</li> </ul> <p>If any of these conditions appear for the first time while using <i>{Invented name}</i>, the woman should stop using it at once and consult her doctor immediately.</p> <p>The product should be used with caution and after a risk/benefit evaluation regarding the individual patient if she has ever had any of the following problems:</p> <ul style="list-style-type: none"> <li>• increased risk of developing blood clots</li> </ul> |

| Risk | What is known   | Preventability  |
|------|---|---|
|      | <p>long term treatment with a medicine used to prevent blood clots</p> <ul style="list-style-type: none"> <li>• if one of the woman's close relatives ever had a blood clot in the leg, lung (pulmonary embolism), or other organ</li> <li>• if the woman has systemic lupus erythematosus (SLE)</li> <li>• if the woman has cancer.</li> </ul> <p>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.</p> <p>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).</p> <p>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).</p> <p>Vascular occlusion can also occur in an artery. If the blood clot forms in an artery, it can cause serious problems, for example heart attack (if the clot forms in the blood vessels of the heart) or stroke (if the clot forms in the vessels of the brain).</p> <p>Women over the age of 60 years who use oestrogen-progestogen HRT are slightly more likely to develop heart disease than those who are not using any HRT.</p> <p>For women who have had their womb removed and are using oestrogen-only therapy there is no increased risk of developing a heart disease.</p> | <ul style="list-style-type: none"> <li>• high blood pressure</li> <li>• diabetes</li> <li>• a very high level of fat in the blood</li> <li>• migraine or severe headache</li> <li>• a disease of the immune system that affects many organs of the body (systemic lupus erythematosus)</li> </ul> <p>If the patient has increased risk of developing blood clots the doctor should be informed about it before starting the treatment, and the patient should see her doctor more often for check-ups.</p> <p>Early detection of the symptoms helps the correct diagnosis in time and improves the clinical outcome.</p> <p>HRT should be stopped and the patient should seek medical advice immediately if any of the following signs of a blood clot are noticed during using HRT:</p> <ul style="list-style-type: none"> <li>• painful swelling and redness of the legs</li> <li>• sudden chest pain, sensation of fullness in the chest which may reach the left arm;</li> <li>• weakness or numbness of the face, arm or leg, especially on one side of the body;</li> <li>• extreme weakness, anxiety, or shortness of breath, difficulty in breathing</li> <li>• discomfort radiating to the back, jaw, throat, arm and stomach;</li> <li>• changes in vision</li> <li>• changes in speech</li> <li>• unexplained migraine-like</li> </ul> |

| Risk   | What is known   | Preventability   |
|--|---|--|
|  | <p>The risk of an arterial blood clot in users of HRT increases:</p> <ul style="list-style-type: none"> <li>• with increasing age</li> <li>• if the woman smokes</li> <li>• if the woman is overweight</li> <li>• if the fat content of the blood is increased (cholesterol or triglycerides)</li> <li>• if the woman has high blood pressure</li> <li>• if one of the woman's close relatives ever had a stroke at a young age</li> <li>• if the woman suffers from migraine</li> <li>• if the woman has a problem with her heart (valve disorder, a disturbance of the cardiac rhythm)</li> </ul> <p>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.</p> <p>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.</p> <p>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).</p> | <p>headaches which happen for the first time, as this could be a sign of a stroke</p> <ul style="list-style-type: none"> <li>• loss of consciousness or fainting with or without seizure, loss of balance or coordination;</li> <li>• rapid or irregular heartbeats</li> <li>• a large rise in the patient's blood pressure (symptoms may be headache, tiredness, dizziness).</li> </ul> <p>As a further precaution measure (as a general rule in all patients who are undergoing major surgeries), prophylactic measures need to be considered to prevent developing blood clots following surgery. If a prolonged immobilisation is needed after a planned surgery, temporarily stopping of the hormone replacement therapy 4 to 6 weeks before the surgery is recommended. Treatment should not be restarted until the woman is completely mobilised.</p> |
| <p><b>Thickening the inner lining of the womb / Tumor development from the inner lining of the womb</b><br/>(Endometrial hyperplasia / Endometrial cancer)</p> | <p>Endometrial hyperplasia is a condition of excessive growth of the cells of the inner lining of the uterus (endometrium). Most cases of endometrial hyperplasia result from high levels of estrogens, combined with insufficient levels of the progesterone-like hormones. Most cases of endometrial</p>  | <p>Taking a progestogen in addition to the oestrogen for at least 12 days of each 28 day cycle protects woman from the risk of endometrial hyperplasia and endometrial cancer. So progestogen will be prescribed separately for women who still have womb. Careful monitoring (including sampling of the inner</p>   |

| Risk | What is known   | Preventability   |
|------|---|--|
|      | <p>hyperplasia are benign, or noncancerous. Because of the associated hormonal changes, this condition is most common among women who are nearing menopause or have reached menopause. Endometrial hyperplasia is a significant risk factor for the development or even co-existence of endometrial cancer.</p> <p>Endometrial cancer refers to several types of malignancies that arise from the lining of the uterus (endometrium). Endometrial cancers are the most common gynecologic cancers in developed countries, with over 142,200 women diagnosed each year. Endometrial cancer is the third most common cause of gynecologic cancer death (behind ovarian and cervical cancer). Complete surgical removal of the uterus with the removal of the ovaries and uterine tubes of both sides is the most common therapeutic approach.</p> <p>Using oestrogen-only hormone replacement therapies will increase the risk of excessive thickening of the lining of the womb (endometrial hyperplasia) and cancer of the womb lining (endometrial cancer).</p> <p>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.</p> <p>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</p> | <p>lining of the uterus when indicated to rule out malignancies) and treatment of women with endometrial hyperplasia is essential to prevent and detect early endometrial cancer.</p> <p>Although women may have irregular bleeding or drops of blood (spotting) during the first 3-6 months of using <i>{Invented name}</i>, they should consult with their doctor if the irregular bleeding:</p> <ul style="list-style-type: none"> <li>• carries on for more than the first 6 months</li> <li>• starts after they have been using <i>{Invented name}</i> for more than 6 months</li> <li>• carries on after they have stopped using <i>{Invented name}</i></li> <li>• or if they have painful menstrual periods</li> </ul> <p>The patient should tell her doctor before starting treatment if she has ever had any of the following problems, as these may return, or become worse during treatment with <i>{Invented name}</i>:</p> <ul style="list-style-type: none"> <li>• fibroids or other benign growths tumours of the womb, growth of womb lining outside your womb (endometriosis) or a history of excessive growth of the womb lining (endometrial hyperplasia)</li> <li>• increased risk of getting an oestrogen-sensitive cancer (such as having a mother, sister or grandmother who has had oestrogen-sensitive cancer)</li> </ul> |

| Risk  | What is known  | Preventability   |
|---|--|--|
|   | <p>cancer (i.e. between 5 and 55 extra cases), depending on the dose and for how long it is taken.</p>   | <p>As a precaution measure, <i>{Invented name}</i> should not be used, if the woman:</p> <ul style="list-style-type: none"> <li>• has or has ever had any cancer which is sensitive to oestrogens, such as cancer of the lining of the womb (endometrium), or if she is suspected of having it;</li> <li>• has any unexplained vaginal bleeding;</li> <li>• has excessive thickening of the lining of the womb (endometrial hyperplasia) and she has not been treated for this yet.</li> </ul> <p>If any of these conditions appear for the first time while using <i>{Invented name}</i> the woman should stop using it at once and consult her doctor immediately.</p> |
| <p><b>Breast cancer</b><br/>(Breast cancer)</p> | <p>Breast cancer is a type of cancer originating from breast tissue, most commonly from the inner lining of milk ducts or the lobules that supply the ducts with milk.</p> <p>Evidence suggests that using combined oestrogen-progestogen and possibly also oestrogen-only hormone replacement therapies increases the risk of breast cancer. The extra risk depends on how long the woman takes HRT. However, it returns to normal within a few years (at most 5) after stopping treatment.</p> <p>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.</p> <p>Women aged 50 to 79 who are</p> | <p>Lifestyle changes have been shown in studies to decrease breast cancer risk by maintaining a healthy body weight, getting regular physical activity, avoiding or limiting alcohol intake and quitting smoking.</p> <p>As a precaution measure, <i>{Invented name}</i> should not be used, if the woman has or ever had breast cancer, or if she is suspected of having it.</p> <p>The product should be used with caution and after a risk/benefit evaluation regarding the individual patient if she has an increased risk of getting an oestrogen-sensitive cancer (such as having a mother, sister or grandmother who has had breast cancer)</p>                   |

| Risk  | What is known  | Preventability   |
|---|--|--|
|   | <p>not using HRT, on average, 9 to 14 in 1000 will be diagnosed with breast cancer over a 5-year period.</p> <p>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).</p>   | <p>Early detection will not prevent breast cancer, but it can help find it when the likelihood of a successful treatment is greatest.</p> <p>Regular self-check of the breast is important for an early detection of breast cancers. Patients should consult with their doctor if they notice any changes such as dimpling of the skin, changes in the nipple or any lumps they can see or feel. Breast cancer screening is recommended regularly.</p>   |
| <p><b>Ovarian cancer</b><br/>(Ovarian cancer)</p> | <p>Ovarian cancer is cancer that begins in the ovaries. Ovaries are reproductive glands found only in women. The ovaries produce eggs (ova) for reproduction. The ovaries are also the main source of the female hormones estrogen and progesterone.</p> <p>Ovarian cancer that are not benign are malignant (cancerous) or low malignant potential tumors. These types can spread to other parts of the body and can be fatal.</p> <p>Ovarian cancer is rare. A slightly increased risk of ovarian cancer has been reported in woman using HRT for at least 5 to 10 years.</p> <p>The risk of ovarian cancer in users of HRT increases:</p> <ul style="list-style-type: none"> <li>• with increasing age</li> <li>• in overweight patients</li> <li>• if the patient had already gone through menopause</li> <li>• if the patient has no children</li> <li>• if the patient's mother, sister</li> </ul> | <p>Ovarian cancer may cause several signs and symptoms. Women are more likely to have symptoms if the disease has spread beyond the ovaries, but even early stage ovarian cancer can cause them. The most common symptoms include:</p> <ul style="list-style-type: none"> <li>• Bloating</li> <li>• Pelvic or abdominal pain</li> <li>• Trouble eating or feeling full quickly</li> <li>• Urinary symptoms such as urgency (always feeling like you have to go) or frequency (having to go often)</li> <li>• Fatigue</li> <li>• Upset stomach</li> <li>• Back pain</li> <li>• Pain during sex</li> <li>• Constipation</li> <li>• Menstrual changes</li> <li>• Abdominal swelling with weight loss</li> </ul> |

| Risk  | What is known  | Preventability  |
|---|--|---|
|   | <p>or daughter has or ever had ovarian or breast cancer</p> <ul style="list-style-type: none"> <li>• if the patient ever had breast cancer</li> <li>• if the patient had been on estrogen replacement therapy without progesterone for more than 5 years</li> <li>• if the patient or anyone in her family has a BRCA( breast cancer) gene mutation</li> <li>• if the patient or anyone in her family has a colorectal cancer</li> </ul>   | <p>These symptoms are also commonly caused by benign diseases and by cancers of other organs. When they are caused by ovarian cancer, they tend to be persistent and represent a change from normal – for example, they occur more often or are more severe.</p> <p>There are no effective and proven screening tests for early detection of ovarian cancer, but there are things what the patient can do.</p> <p>Watching for and reporting the above mentioned signs and symptoms may allow earlier detection. Although all these symptoms can have other causes, if a woman has these symptoms almost daily for more than a few weeks, she should see her doctor, preferably a gynecologist.</p> |
| <p><b>Unintentional Secondary Exposure</b><br/>(Unintentional Secondary Exposure)</p> | <p>The estrogen in <i>{Invented name}</i> can be accidentally transferred from the area of skin where it was sprayed to other people. Young children who are accidentally exposed to estrogen through contact with women using <i>{Invented name}</i> may show signs of puberty that are not expected (for example, breast budding).</p> <p>In case of signs and symptoms (breast development or other sexual changes) in a child that may have occurred through accidental exposure to <i>{Invented name}</i>, it should be stopped and healthcare provider should be informed. In most cases the child's breasts will go back to normal when they are no longer exposed to Estradiol transdermal</p> |   |



| Risk | What is known   | Preventability |
|------|---|----------------|
|      | <p>spray.</p> <p>In order to prevent estradiol transfer, it is important to try to avoid others, especially children, to come into contact with the exposed area of the woman's skin where she sprayed <i>{Invented name}</i>. For this reason, women should not allow other people to touch the area of skin they have sprayed for at least 60 minutes afterwards. If another persons accidentally touches the area of the skin where the woman sprayed <i>{Invented name}</i>, it should be advised them to wash the area of their skin with soap and water right away. If the patient gets <i>{Invented name}</i> spray on another area of her skin like her hands, she should wash that area of her skin with soap and water right away.</p> <p>Small pets may be especially sensitive to the estrogen in <i>{Invented name}</i>. For this reason it is advised not to allow pets to lick or touch the arm where <i>{Invented name}</i> was sprayed. If the pets shows signs of nipple and/or vulvar enlargement, or any other signs of illness veterinarian should be contacted.</p> |                |

### Important potential risks

| Risk  | What is known (Including reason why it is considered a potential risk)  |
|---|---|
| <p><b>Medication error (Overdose)</b><br/>(Medication error (Overdose))</p> | <p>Serious ill effects have not been reported following acute ingestion of large doses of estrogen-containing products by young children. In case of using more <i>{Invented name}</i> or if children have been using the medicine by accident, feeling sick, vomiting and withdrawal bleeding (unusual vaginal bleeding) may occur. If it happens the doctor or the hospital should be informed to get an opinion of the risk and advice</p> |

| Risk   | What is known (Including reason why it is considered a potential risk)   |
|--|--|
|  | on action to be taken.   |
| <b>Allergic reaction to octisalate</b><br>(Hypersensitivity to octisalate) | <p>Like all medicines, <i>{Invented name}</i> can cause allergic reactions in patients who are susceptible for such events.</p> <p>Patients should always inform their doctors about any allergies they have before starting the treatment with this product.</p> <p>Patients should be advised to remain vigilant for any symptoms compatible with an allergic reaction (e.g. difficulty in breathing, wheezing, dizziness, swelling of the face or throat (angioedema), itching, hives (general or localised rash or lumps), skin irritations or swelling, etc.) and to stop <i>{Invented name}</i> and seek medical advice immediately if such symptoms occur.</p> <p>Patients who are allergic to estradiol octasialate or any of the other ingredients of this medicine must not use Estradiol transdermal spray.</p> |

### Missing information

| Risk  | What is known  |
|---|--|
| <b>Application site reactions</b><br>(Application site reactions) | <p>Like all medicines, <i>{Invented name}</i> can cause allergic reactions in patients who are susceptible for such events.</p> <p>Patients should always inform their doctors about any allergies they have before starting the treatment with this product. Patients who are allergic to estradiol octasialate or any of the other ingredients of this medicine must not use Estradiol transdermal spray.</p> <p>Patients should be advised to remain vigilant for any symptoms compatible with a local allergic reaction (e.g. rash, itching, hives (localised rash or lumps), skin irritations or swelling, etc.). The following reactions also have been reported with other hormone replacement therapies: discoloration of the skin especially of the face or neck known as “pregnancy patches” (chloasma), painful reddish skin nodules (erythema nodosum), rash with target-shaped reddening or sores (erythema multiforme). Patient advised to stop <i>{Invented name}</i> and seek medical advice immediately if such symptoms occur.</p> |
| <b>Long term use</b><br>(Long term use)                           | <p><i>{Invented name}</i> is hormone replacement therapy (HRT). The use of HRT carries risks which need to be considered when deciding whether to start using and once it was started, regular check-ups are needed. During these check-ups the</p>  |

| Risk | What is known   |
|------|---|
|      | <p>benefits and risks should be discussed with the doctor.</p> <p>Evidence regarding risks associated with HRT in the treatment during long term use is limited. For this reason the long term safety of the product is consider as missing information, although estradiol is a well-known active substance and octisalate is a common ingredient of sunscreen, mainly used for short-time. Please see the Endometrial hyperplasia/endometrial cancer, Breast cancer, Ovarian cancer and Application site reactions chapters of this section above concerning the potential effect of HRTs during long term use.</p> |

### ***VI.2.5 Summary of additional risk minimisation measures by safety concern***

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL)/ patient information leaflet (PIL). The measures in these documents are known as routine risk minimisation measures.

Appropriate labelling is planned for the management of all the above listed safety concerns of Gedeon Richter Plc.'s product of *{Invented name}*.

The Summary of Product Characteristics and the Package Leaflet of *{Invented name}* can be found in "***Annex 2 - SmPC & Package Leaflet***".

*{Invented name}* has no additional risk minimisation measures

### ***VI.2.6 Planned post authorisation development plan (if applicable)***

No post-authorisation studies/activities are planned by Gedeon Richter Plc. for its product of *{Invented name}* containing estradiol hemihydrate.

### ***VI.2.7 Summary of changes to the risk management plan over time***

Not applicable, since this is the first RMP on Gedeon Richter Plc's product of *{Invented name}* containing estradiol hemihydrate as a transdermal spray.