6.1 Elements for a public summary

6.1.1 Overview of disease epidemiology

What is menopause and what does it lead to?

Menopause is a normal event in a woman's life that marks the permanent end of her menstrual period. Typically, a woman will start experiencing menopause between the age of 48 and 51.

Menopause leads to many changes in the body; the main change is a fall in the levels of the female sex hormone, oestrogen.

Oestrogen is responsible for many functions including taking care of the growth and thickness of the womb, keeping the vagina healthy and moist, and even maintaining blood supply to the skin.

Fall in oestrogen levels also results in a woman developing osteoporosis. Osteoporosis is a serious disease of the bone that makes the bones weak, causing them to break easily.

What are the symptoms of oestrogen deficiency?

When the oestrogen level falls during menopause, the woman starts experiencing symptoms that could cause her a lot of discomfort. Some of the symptoms of oestrogen deficiency are:

- Hot flushes
- Sweats
- Vaginal dryness

Who will experience these symptoms?

About 80% of women who go through menopause will have these symptoms. Most women will experience vaginal atrophy after menopause; however, only half of the women with this condition will show any related symptoms. Hot flushes are the most common symptom seen during this time. Women could have hot flushes as early as 2 years before periods stop and as late as up to 5-10 years after periods stop. A higher chance of experiencing these symptoms is seen in women whose periods stop early, women who normally have low levels of oestrogen and women who smoke.

About 1 out of every 3 women in the Unites States and Europe will suffer from osteoporosis. At least 40% of them will have one fracture in their lifetime.

6.1.2 Summary of treatment benefits

What is used to treat symptoms of oestrogen deficiency?

Treatment for symptoms of menopause can act locally, like vaginal lubricants and moisturises, and vaginal preparations containing oestrogens, that are used to treat vaginal symptoms. Treatments can also act by supplying oestrogen to the entire body, for symptoms like hot flushes, sweats and vaginal symptoms. These treatments are taken as tablets or as skin patches.

Osteoporosis can be prevented with medicines or through lifestyle changes like starting a balanced diet with an adequate intake of calcium, exercise, preventing falls, stopping smoking and reducing drinking.

Where does Activelle® Low Dose fit in?

Activelle® Low Dose is a tablet which is taken orally and contains both oestrogen and a progestagen. The oestrogen component in Activelle® Low Dose (estradiol) provides relief from the symptoms of oestrogen deficiency, like hot flushes, night sweats and vaginal dryness, while the other component, a progestagen (norethisterone acetate) protects the lining of the womb against excessive growth caused by oestrogen.

If you are in the U.S., you could also be prescribed Activelle® Low Dose for the prevention of osteoporosis.

What studies have been done with Activelle® Low Dose?

A total of 218 postmenopausal women have been treated with Activelle® Low Dose in 2 main clinical trials. The studies have shown that Activelle® Low Dose provides sufficient oestrogen to relieve the unpleasant symptoms of menopause, with the additional benefit of protecting the lining of the womb from harmful effects of medication.

6.1.3 Unknowns relating to treatment benefits

Activelle® Low Dose and the higher-dosed Activelle® have been on the market for a long time. The product has also been well-studied for the approved indications. The benefits and safety of Activelle® Low Dose are well-established and are in accordance with the product label.

6.1.4 Summary of safety concerns

A summary of the important identified and potential risks concerning treatment with Activelle® Low Dose are described Table 6-3 and Table 6-4 respectively.

Table 6-3 Summary of safety concerns – Important identified risks

Risk	What is known	Preventability
Cancers which are sensitive to oestrogen such as breast cancer, cancer of the womb lining (endometrium) and ovarian cancer (Oestrogen-dependent malignancies [breast cancer, endometrial cancer, ovarian cancer])	Postmenopausal women treated with hormonal therapy have an increased risk of developing some cancers, such as breast cancer, endometrial cancer and ovarian cancer; this may be related to high levels of E_2 in the blood.	Activelle® Low Dose should not be used in women who have had a history or possess the risk of developing breast or endometrial cancer. A doctor should be consulted immediately if there is any breakthrough vaginal bleeding. Regularly check your breasts and see a doctor if you notice any changes such as: • dimpling of the skin • changes in the nipple • any lumps you can see or feel
Blood clots in the vein, such as in the legs or the lungs (Venous thromboembolism [deep venous thrombosis, pulmonary embolism])	The risk of developing blood clots in veins increases after treatment with oral oestrogen therapy. These blood clots can be serious, and if one travels to the lungs, it can cause chest pain, breathlessness and fainting.	Activelle® Low Dose should not be used in women who have or have ever had a blood clot in the vein, such as in the legs (DVT) or the lungs (pulmonary embolism). It should also not be used in women who have a blood clotting disorder. A doctor should be consulted immediately if you notice signs of a blood clot, such as: • painful swelling and redness of the legs • sudden chest pain • difficulty in breathing
Heart disease (Coronary artery disease)	Women over the age of 60 years who use hormonal treatment (oestrogen with another female hormone called progestagen) are slightly more likely to develop heart disease than those not taking any hormonal treatment.	Activelle® Low Dose should not be used in women who have or have ever had a heart disease caused by blood clots in the arteries. A doctor should be consulted if there is a large rise in your blood pressure and you experience chest pain, abnormal heart beats or significant tiredness.
Ischaemic stroke	The risk of getting a stroke is higher in women taking hormonal treatment than in those not taking any hormonal treatment. In addition, the number of extra cases of stroke due to use of hormonal treatment increases with age.	Activelle® Low Dose should not be used in women who have or have ever had a stroke. A doctor should be consulted if you experience headache, dizziness, and tiredness.

Abbreviations: E_2 = estradiol; DVT = deep vein thrombosis.

Table 6-4 Summary of safety concerns – Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Hypersensitivity reactions	Activelle® Low Dose can cause hypersensitivity reactions in some women if they are allergic to the active ingredients (E_2/NETA) or any other excipients of this medicine. Do not use Activelle® Low Dose if you are allergic to any of the ingredients of this medicine.

Abbreviations: E_2 = estradiol; NETA = norethisterone acetate.

Table 6-5 Summary of safety concerns – Important missing information

Risk	What is known
None	

6.1.5 Summary of additional risk minimisation measures by safety concern

There are no additional risk minimisation measures for any of the safety concerns.

6.1.6 Planned post-authorisation development plan

There are no post-authorisation safety or efficacy studies planned for Activelle® Low Dose.

6.1.7 Summary of changes to the risk management plan over time

The changes to the risk management plan over time is summarised in 6-6.

Table 6-6 Major changes to the risk management plan over time

Version	Date	Safety concerns	Comment
Edition 1, Version 1	06 Jul 2007	**Important identified risks** (class effects: breast cancer, cardiovascular disease, vaginal bleeding) **Important potential risks** (allergic reactions) **Important missing information** (Safety/AE experience in population not covered in the ALD-1537 study)	None
Edition 3, Version 1	19 May 2014	**Vaginal bleeding** Based on results from ADL-3795 and evaluation of post-marketing safety information, vaginal bleeding is no longer considered a safety concern.	Vaginal bleeding deleted as an important identified risk.
		Important missing information No important information regarding the safety of Activelle® Low Dose in the population of postmenopausal women not studied in clinical trials is considered missing.	Important missing information updated to "none"
		PASS ALD-3795 evaluating bleeding profile of Activelle® Low Dose was completed since the last submission of RMP.	Details of study included in the current RMP version.

Note: RMP Edition 2, Version 1 was prepared but not submitted.

Abbreviations: AE = adverse event; PASS = post-authorisation safety study; RMP = risk management plan.