VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

In women in menopausal period, the decrease of hormones (estrogen levels) result in genital areas becoming dry, itchy and more easily irritated. Vaginal atrophy is a frequent complaint of these women.

Symptoms associated with vulvovaginal atrophy (VVA), such as lack of lubrication and pain with intercourse, affect 20% to 45% of midlife and older women.

About 50% of otherwise healthy women over 60 years of age experience symptoms related to urogenital atrophy such as vaginal dryness, dyspareunia, burning, itching, as well as urinary complaints or infections of the lower urinary tract. As these alterations frequently affect the quality of life of postmenopausal women, it is important for doctors to detect their presence and offer treatment options.

VI.2.2 Summary of treatment benefits

Estriol normalizes the vaginal, cervical and urethral epithelium and thus helps to restore the normal microflora and the physiological pH in the vagina. Moreover, estriol increases the resistance of the vaginal epithelial cells to infection and inflammation and decreases the incidence of urogenital complaints.

Estriol, which is an estrogen, can be used in the treatment of vaginal symptoms and complaints (vaginal dryness, itching, discomfort and painful intercourse) due to estrogen deficiency related to menopause (whether naturally or surgically induced).

In a randomized clinical trial versus placebo, intravaginal application of a low dose of estriol (50 micrograms per application) the main endpoint was to evaluate the efficacy of the product by evaluation of the change in the maturation value of the vaginal epithelium after 12 weeks of treatment. In this study, it was shown that it produced a significant improvement in maturation value of vaginal epithelium, vaginal pH and vaginal atrophy signs such as fragility, dryness and pallor of the mucosa and flattening of folds. In the responder analysis by symptom, statistical significance was reached for vaginal dryness, but not for dyspareunia, vaginal pruritus, burning and dysuria, after 12 weeks of treatment.

Gelistrol 50 micrograms/g vaginal gel contains ultra-low estriol dose (ten times lower than those included in the already marketed products) and acts locally at the vagina.

VI.2.3 Unknowns relating to treatment benefits

Gelistrol 50 micrograms/g vaginal gel is indicated in postmenopausal women. Studies on specific types of sub-populations, regarding age (paediatric use), race, concomitant illness or concomitant vaginal treatments are not available.

VI.2.4 Summary of safety concerns

Important identified risks

There has not been identified any important risk.

Important potential risks

Table 1. Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Estrogen dependant breast cancer (the tumour cells require estrogen for growth)	Treatment with estrogens may increase the risk of breast cancer when the hormone in absorbed and goes into blood torrent. As Gelistrol 50 micrograms/g vaginal gel is administered directly in the vagina and has been studied that the amount that is absorbed shown to be almost negligible after repeated administration, such risk is highly unlikely to be produced.
Endometrial hyperplasia (increase in the number of cells of the uterus)	This risk is dependent on the duration of treatment with estrogens and also the dose administered. This risk has not been attributed to treatment with estriol by vaginal use. However, if continued treatment is required, periodical revisions are recommended.
Venous thromboembolic disorder, stroke and coronary artery disease	Treatment with estrogens may increase the risk of presenting with thrombosis, pulmonary embolism, stroke, myocardial infarction etc. when the hormone in absorbed and goes into blood torrent. As Gelistrol 50 micrograms/g vaginal gel is administered directly in the vagina and has been studied that the amount that is absorbed shown to be almost negligible after repeated administration, such risk is highly unlikely to be produced.

Missing information

Table 2. Missing information

Risk	What is known
Interaction with other medicinal products.	No interaction studies between Gelistrol 50 micrograms/g vaginal gel and other medicines have been performed. As Gelistrol is administered locally at a low dose, no clinically relevant interactions are expected. Tell your doctor if you are taking or have recently taken or might take any other medicines, including medicines obtained without a prescription.

VI.2.5 Summary of 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). The measures in these documents are known as routine risk minimisation measures.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post authorisation development plan

Table 3. List of studies in post authorisation development plan

Study / activity Type, title and category	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**
A Phase II prospective, randomized, double-blind, placebo-controlled multi-centre study to assess the safety of vaginal estriol in hormone receptor-positive postmenopausal women with early stage breast cancer in treatment with aromatase inhibitor in the adjunvant setting. "BLISSAFE Study"	The primary objective is to evaluate the levels of FSH after treatment with 0.005% estriol vaginal gel in hormone receptor-positive postmenopausal women with early stage breast cancer in treatment with NSAIs in the adjuvant setting and vaginal atrophy. Plasma levels of estrogens (estradiol, estriol estrone) and LH will also be determined at different timepoints.	Estrogen dependant breast cancer	Study under design. The study is now under documental phase	Second quarter 2016.

Studies which are a condition of the marketing authorisation

Not applicable

VI.2.7 Summary of changes to the Risk Management Plan over time

Changes regarding Important Potential Risk have been performed in this second version as per the MPA request, and new version of the Summary of products Characteristics approved by the MPA has been updated.