SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Blissel 50 micrograms/g vaginal gel

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 g vaginal gel contains 50 micrograms estriol.
Excipients: 1 g vaginal gel contains 1.60 mg of sodium methyl parahydroxybenzoate and 0.20 mg of sodium propyl parahydroxybenzoate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Vaginal gel
Gel homogeneous, colourless, clear to slightly translucent.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Local treatment of vaginal dryness in postmenopausal women with vaginal atrophy.

4.2 Posology and method of administration

Blissel 50 micrograms/g vaginal gel is an estrogen-only product for vaginal use.

Guidance on how to start therapy and maintenance

Blissel can be started any time after the manifestation of atrophic vaginitis.

Initial treatment: One applicator-dose of vaginal gel per day for 3 weeks (suitably at bedtime).
As maintenance treatment one applicator-dose of vaginal gel twice a week (suitably at bedtime) is recommended. An evaluation of treatment continuation after 12 weeks should be carried out by the physician.

For initiation and continuation of treatment of post- menopausal symptoms, the lowest effective dose for the shortest duration (see also Section 4.4) should be used.

A missed dose should be administered as soon as remembered, unless it is more than 12 hours overdue. In the latter case the missed dose should be skipped and the next dose should be administered at the normal time.

Administration:

Blissel has to be applied into the vagina using a dose-marked applicator, following carefully “Instructions for use” included in the information leaflet, and below.

One applicator-dose (applicator filled to the mark) delivers a dose of 1 g vaginal gel containing 50 micrograms of estriol. The filled applicator should be inserted into the vagina and emptied, preferably in the evening.

To apply the gel, lie down, with knees bent and spread apart. Gently insert the open end of the applicator deep into the vagina and slowly push the plunger all the way down, as far as it will go to empty the gel into the vagina.

After use, pull the plunger out of the cannula and then, accordingly with the presentation, you may clean or reject the cannula as indicated in "Instructions for use" included in the information leaflet.

4.3 Contraindications

- Known, past or suspected breast cancer
- Known or suspected estrogen-dependent malignant tumour (e.g. endometrial cancer)
- Undiagnosed genital bleeding
- Untreated endometrial hyperplasia
- Previous idiopathic or current venous thromboembolism (deep venous thrombosis, pulmonary embolism)
- Active or recent arterial thromboembolic disease (e.g. angina, myocardial infarction)
- Known thrombophilic disorders (e.g. protein C, protein S, or antithrombin deficiency, see section 4.4);
- Acute liver disease or a history of liver disease as long as liver function tests have failed to return to normal
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Porphyria

4.4 Special warnings and precautions for use

For the treatment of postmenopausal symptoms, local estrogen therapy should only be initiated for symptoms that adversely affect quality of life.

In all cases, a careful appraisal of the risks and benefits should be undertaken at least annually and HRT should only be continued as long as the benefit outweighs the risk.

Blissel 50 micrograms/g vaginal gel must not be combined with estrogen preparations for systemic treatment, as there are no studies of safety and risks with estrogen concentrations attained in combination treatment.

Intravaginal applicator may cause minor local trauma, especially in women with serious vaginal atrophy.

Warning about excipients

Blissel 50 micrograms/g vaginal gel contains sodium methyl parahydroxibenzoate (E 219) and sodium propyl parahydroxibenzoate (E 217). May cause allergic reactions (possibly delayed).

Medical examination/follow-up of treatment

Before estriol treatment is initiated or reinstituted, a complete personal and family medical history should be taken. Physical (including pelvic and breast) examination should be guided by this and

by the contraindications and warnings for use. During treatment, periodic check-ups are recommended with a frequency and nature adapted to the individual woman. Women should be advised of which changes in their breasts should be reported to their doctor or nurse (see 'Breast cancer' below).
Investigations, including mammography, should be carried out in accordance with currently accepted screening practices, modified to the clinical needs of the individual.
In case of vaginal infections, these should be treated before starting therapy with Blissel 50 micrograms/g vaginal gel.

Conditions which need supervision

If any of the following conditions are present, have occurred previously and/or have been aggravated during pregnancy or previous hormone treatment, the patient should be closely supervised. It should be taken into account that these conditions may recur or be aggravated during treatment with Blissel 50 micrograms/g vaginal gel, in particular:

- Leiomyoma (uterine fibroids) or endometriosis
- Risk factors for thromboembolic disorders (see section "Venous thromboembolic disorder" below)
- Risk factors for estrogen-dependent tumours, e.g. first degree heredity for breast cancer
- Hypertension
- Liver disorders (e.g. liver adenoma)
- Diabetes mellitus with or without vascular involvement
- Cholelithiasis
- Migraine or (severe) headache
- Systemic lupus erythematosus (SLE)
- A history of endometrial hyperplasia (see section "endometrial hyperplasia")
- Epilepsy
- Asthma
- Otosclerosis

Reasons for immediate withdrawal of treatment

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

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

Blissel is a locally acting low dose estriol preparation and therefore the occurrence of the conditions mentioned below is less likely than with systemic oestrogen treatment.

Endometrial hyperplasia and carcinoma

The risk of endometrial hyperplasia and carcinoma in peroral treatment solely with estrogen is dependent on both the duration of treatment and the dose of estrogen. An increased risk of endometrial hyperplasia or uterine cancer has not been attributed to treatment with estriol by vaginal use. However, if continued treatment is required, periodical revisions are recommended, with special consideration given to any symptoms suggestive of endometrial hyperplasia or endometrial malignancy.

If breakthrough bleeding or spotting appears at any time on therapy, the reason should be investigated which may include endometrial biopsy to exclude endometrial malignancy.

Unopposed estrogen stimulation may lead to premalignant transformation in the residual foci of endometriosis. Therefore, caution is advised when using this product in women who have undergone hysterectomy because of endometriosis, especially if they are known to have residual endometriosis.

Breast, uterine and ovarian cancer

Systemic treatment with estrogens may increase the risk of certain types of cancer, in particular uterine, ovarian and breast cancer. Blissel 50 micrograms/g vaginal gel administered locally that contains a low dose of estriol is not expected to increase the risk of cancer.

Venous thromboembolic disorder, stroke and coronary artery disease

Hormone replacement treatment with preparations with systemic effect is associated with an increased risk of venous thromboembolism (VTE), stroke and coronary artery disease. Blissel 50 micrograms/g vaginal gel, which contains a low dose of estriol for local treatment, is not expected to give an elevated risk of VTE, stroke and coronary artery disease.

Generally recognised risk factors for VTE include a personal history or family history, severe obesity (BMI > 30 kg/m^2) and systemic lupus erythematosus (SLE). There is no consensus about the possible role of varicose veins in VTE. Closely supervision is recommended in these patients.

Other conditions

Estrogens with systemic effects may cause fluid retention or increase of plasma tryglicerides, for which reason, patients with heart diseases or impaired renal function or with preexisting hypertriglyceridemia, respectively, should be carefully observed during the first weeks of treatment. Blissel 50 micrograms/g vaginal gel contains a low dose of estriol for local treatment, therefore systemic effects are not expected.

Patients suffering from severe renal insufficiency /should be carefully observed, as it may be expected that the level of circulating estriol is increased.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies between Blissel 50 micrograms/g vaginal gel and other medicines have been performed. As Blissel is administered locally at a low dose, no clinically relevant interactions are expected.

4.6 Fertility, pregnancy and lactation

Pregnancy
Blissel 50 micrograms/g vaginal gel is not indicated during pregnancy.
If pregnancy occurs during treatment with Blissel 50 micrograms/g vaginal gel, treatment shall be withdrawn immediately.
For estriol no clinical data on exposed pregnancies are available.
The results of most epidemiological studies to date relevant to inadvertent foetal exposure to estrogens indicate no teratogenic or foetotoxic effects.

Breastfeeding
Blissel 50 micrograms/g vaginal is not indicated during lactation.

4.7 Effects on ability to drive and use machines

Blissel 50 micrograms/g vaginal gel has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Undesirable effects from estriol are usually reported in 3-10% of those patients who are treated. They are often transient and of mild intensity.

At the beginning of treatment, when the mucous membrane in the vagina is still atrophic, local irritation may occur in the form of a sensation of heat and/or itching.

The undesirable effects found in the clinical studies performed with Blissel 50 micrograms/g vaginal gel have been classified according to frequency of appearance:

Organ System Class	Common (≥ 1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1000)
Reproductive system and breast disorders	Pruritus genital.		
		Pelvic pain, genital rash.	
General disorders and administration site conditions	Application site pruritus		
		Application site irritation	
Infections and infestations		Candidiasis	
Nervous system disorders		Headache	
Skin and subcutaneous tissue disorders	Pruritus		
		Prurigo	

Blissel is a locally administered vaginal gel with a very low dose of estriol and self-limiting systemic exposure (shown to be almost negligible after repeated administration), and as such is highly unlikely to produce the more severe effects associated with oral estrogen replacement therapy. However, other very rare adverse reactions have been reported with higher dose systemic estrogen/progestin therapy. These are:

- Estrogen-dependent neoplasms benign and malignant, e.g. endometrial cancer and breast cancer (see also section 4.3 Contraindications and 4.4. Special warnings and precautions for use)

- Venous thromboembolism, i.e. deep leg or pelvic venous thrombosis and pulmonary embolism, is more frequent among hormone replacement therapy users than among non-users. For further information, see section 4.3 Contraindications and 4.4. Special warnings and precautions for use

- Myocardial infarction and stroke

- Gall bladder disease

- Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura

- Probable dementia

Reporting of suspected adverse reactions in UK:
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Toxicity for estriol is very low. Overdose of Blissel 50 micrograms/g vaginal gel with vaginal application is very unlikely. Symptoms that may occur in the case of a high dose is accidentally ingested are nausea, vomiting and vaginal bleeding in females. There is no known specific antidote. If necessary, a symptomatic treatment should be instituted.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Estrogens, ATC code: G03CA04.

Blissel 50 micrograms/g vaginal gel contains synthetic estriol, which is chemically and biologically identical to human estriol. Estriol exerts their pharmacological and biological effects through its action on estrogen receptors (ER). Estriol has a high relative binding affinity for estrogen receptors in the bladder and vaginal tissue and a relatively low binding affinity to endometrial and breast tissue estrogen receptors. For this reason, the estriol binding to the endometrial estrogen receptor is too short to induce true proliferation when estriol is given once daily, while its binding to the vaginal estrogen receptor is sufficient to exert a full vaginotrophic effect despite of using very low dose of estriol.

In postmenopausal women, the decrease of estrogen levels result in genital areas becoming dry, itchy and more easily irritated. Local vaginal estriol works directly on the estrogen-sensitive tissues of the lower genito-urinary tract, relieving the symptoms of vaginal atrophy. Estriol induces normalization of 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 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) produces 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 (secondary endpoint), statistical significance was reached for vaginal dryness, but not for dyspareunia, vaginal pruritus, burning and dysuria, after 12 weeks of treatment.

5.2 Pharmacokinetic properties

After single administration of Blissel 50 microgram/g vaginal gel, estriol is readily absorbed and peak estriol plasma concentrations of 106±63 pg/mL were reached at 2 (range 0.5 – 4) h. After the peak, estriol plasma concentrations decrease mono-exponentially with an average half-life of 1.65 ± 0.82 h.

After 21 days of repeated treatment with Blissel, the absorption declines significantly and systemic exposure to estriol is almost negligible. Estriol levels were below the limit of quantitation for all subjects investigated 24 h post-dose.

Nearly all (90%) estriol is bound to albumin in the plasma and estriol is hardly bound to sex hormone-binding globulin (SHBG). The metabolism of estriol consists mainly of conjugation and deconjugation during enterohepatic circulation. Estriol, is mainly excreted by the urine in the conjugated form. Only a small fraction (≤2%) is excreted via the faeces, mainly as unconjugated estriol.

5.3 Preclinical safety data

The toxicological properties of estriol are well known. There is no preclinical data of relevance to the assessment of safety beyond that which has already been considered in other sections of the summary of product characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glycerol (E422)
Sodium methyl parahydroxybenzoate (E 219)
Sodium propyl parahydroxybenzoate (E 217)
Polycarbophil
Carbopol
Sodium hydroxide (for pH-adjustment)
Hydrochloric acid (for pH-adjustment)
Purified water.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store below 25ºC.

6.5 Nature and contents of container

Not all pack sizes may be marketed

Aluminium tubes of 10 and 30 g.

In the case of 10g pack size the tube of 10g is packaged in an outer cardboard box together with the patient information leaflet and may be provided in two presentations:

- 1 sealed blister containing 10 disposable cannula with a filling mark and 1 reusable plunger or
- 1 sealed bag containing 1 reusable cannula with a filling mark and 1 reusable plunger.

In the case of 30g pack size, the tube is also packaged in an outer cardboard box together with the patient information leaflet and may be provided in two presentations:

- 3 sealed blisters containing each 10 disposable cannula with a filling mark and 1 reusable plunger or
- 1 sealed bag containing 1 reusable cannula with a filling mark and 1 reusable plunger.

6.6 Special precautions for disposal

No special requirements.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Italfarmaco S.A.
San Rafael 3
28108 Alcobendas (Madrid)
Spain

8 MARKETING AUTHORISATION NUMBER(S)

PL 20663/0003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10/3/2017