SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Blissel 50 microgram/g, gel voor vaginaal gebruik

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

Treatment of symptoms of vaginal atrophy due to oestrogen deficiency in postmenopausal women

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.

For oestrogen products for vaginal application of which the systemic exposure to the oestrogen remains within the normal postmenopausal range, it is not recommended to add a progestagen (but see section 4.4).
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

- In women with an intact uterus the risk of endometrial hyperplasia and carcinoma is increased when **systemic** oestrogens are administered alone for prolonged periods.For oestrogen products for vaginal application of which the systemic exposure to oestrogen remains within the normal postmenopausal range, it is not recommended to add a progestagen.
- Endometrial safety of long-term (more than one year) or repeated use of local vaginally administered oestrogen is uncertain. Therefore, if repeated, treatment should be reviewed at least annually.

- If 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.

The following risks have been associated with systemic HRT and apply to a lesser extent for oestrogen products for vaginal application of which the systemic exposure to the oestrogen remains within the normal postmenopausal range. However, they should be considered in case of long term or repeated use of this product

Breast cancer

Epidemiological evidence from a large meta-analysis suggests no increase in risk of breast cancer in women with no history of breast cancer taking low dose vaginally applied oestrogens. It is unknown if low dose vaginal oestrogens stimulate recurrence of breast cancer.

Ovarian cancer

Ovarian cancer is much rarer than breast cancer. Epidemiological evidence from a large meta-analysis suggests a slightly increased risk in women taking oestrogen-only systemic HRT, which becomes apparent within 5 years of use and diminishes over time after stopping.

Venous thromboembolism

- Systemic HRT is associated with a 1.3-3 fold risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of HRT than later (see Section 4.8).

- Patients with known thrombophilic states have an increased risk of VTE and HRT may add to this risk. HRT is therefore contraindicated in these patients (see section 4.3)

- Generally recognised risk factors for VTE include, use of oestrogens, older age, major surgery, prolonged immobilisation a personal history or family history, obesity (BMI > 30 kg/m2), pregnancy/postpartum period, systemic lupus erythematosus (SLE), and cancer. There is no consensus about the possible role of varicose veins in VTE.

Coronary artery disease (CAD))

Hormone replacement treatment with preparations with systemic effect is associated with an increased risk of coronary artery disease.

Ischaemic stroke

Hormone replacement treatment with preparations with systemic effect is associated with an increased risk of Ischaemic stroke. However, as the baseline risk of stroke is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age (see section 4.8).

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.

Exogenous estrogens may induce or exacerbate symptoms of hereditary and acquired angioedema

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.
Due to the vaginal administration and minimal systemic absorption, it is unlikely that any clinically relevant drug interactions will occur with Blissel. However, interactions with other locally applied vaginal treatments should be considered.

4.6 Fertility, pregnancy and lactation

Fertility
No fertility data available

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.

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.

Class effects associated with systemic HRT

The following risks have been associated with systemic HRT and apply to a lesser extent for oestrogen products for vaginal application of which the systemic exposure to estrogen remains within the normal postmenopausal range.

Ovarian cancer

Use of **systemic** HRT has been associated with a slightly increased risk of having ovarian cancer diagnosed (see Section 4.4).

A meta-analysis from 52 epidemiological studies reported an increased risk of ovarian cancer in women currently using systemic HRT compared to women who have never used HRT (RR 1.43, 95% CI 1.31-1.56). For women aged 50 to 54 years taking 5 years of HRT, this results in about 1 extra case per 2000 users. In women aged 50 to 54 who are not taking HRT, about 2 women in 2000 will be diagnosed with ovarian cancer over a 5-year period.

Risk of venous thromboembolism

Systemic HRT is associated with a 1.3-3-fold increased relative risk of developing venous thromboembolism (VTE), i.e. deep vein thrombosis or pulmonary embolism. The occurrence of such an event is more likely in the first year of using HT (see section 4.4). Results of the WHI studies are presented:

WHI Studies - Additional risk of VTE over 5 years' use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio and 95%CI	Additional cases per 1000 HRT users
Oral oestrogen-only*2			

50 -59	7	1.2 (06.-2.4)	1 (3-10)

*Study in women with no uterus

Risk of ischaemic stroke

- The use of **systemic** HRT is associated with an up to 1.5 fold increased relative risk of ischaemic stroke. The risk of haemorrhagic stroke is not increased during use of HRT.

- This relative risk is not dependent on age or on duration of use, but as the baseline risk is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age, see section 4.4.

WHI studies combined - Additional risk of ischaemic stroke* over 5 years' use

Age range (years)	Incidence per 1000 women in placebo arm over 5 years	Risk ratio and 95%CI	Additional cases per 1000 HRT users
50 -59	8	1.3 (1.1.-1.6)	3 (1-5)

*no differentiation was made between ischaemic and haemorrhagic stroke.

Other adverse reactions have been reported in association with systemic oestrogen/progestagen treatment:

– Gall bladder disease.
– Skin and subcutaneous disorders: chloasma, erythema multiforme, erythema nodosum, vascular purpura.
– Probable dementia over the age of 65

Reporting of suspected adverse reactions
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 Nederlands Bijwerkingen Centrum Lareb at www.lareb.nl.

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.

Treatment of vaginal estrogen deficiency symptoms: Vaginally applied estrogen alleviates the symptoms of vaginal atrophy due to estrogen deficiency in postmenopausal women.

Clinical Efficacy and Safety

The efficacy of Blissel 50 micrograms/g vaginal gel was investigated in a multicenter randomized double blind placebo controlled study in postmenopausal women with symptoms and signs of vulvovaginal atrophy.

Intravaginal application of a low dose of estriol (50 micrograms per application) produced significant improvements in the maturation value of the vaginal epithelium the 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 (p=0.095), 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 21 days of daily treatment with Blissel, the mean peak estriol plasma concentration (± standard deviation) was 22.80 (±15.78) pg/ml. After the peak, estriol plasma concentrations decrease mono-exponentially with an average half-life of 1.65 ± 0.82 h., no accumulation occurs.

Systemic exposure to estriol during twice weekly administration of Blissel was not investigated.

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)
Spanje

8 MARKETING AUTHORISATION NUMBER(S)

RVG 119018

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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