

Public Assessment Report

Scientific discussion

Blissel
(estriol)

SE/H/907/01/DC

This module reflects the scientific discussion for the approval of Blissel. The procedure was finalised at 2010-07-28. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Italfarmaco S.A. has applied for a marketing authorisation for Blissel, vaginal gel, 50 microgram/g. The active substance is estriol. For approved indications, see the Summary of Product Characteristics.

II. QUALITY ASPECTS

II.1 Introduction

Blissel is presented in the form of vaginal gel containing 50 microgram/g estriol. The excipients are polycarbophil, carbopol, glycerol, sodium methyl parahydroxybenzoate, sodium propyl parahydroxybenzoate, hydrochloric acid, sodium hydroxide and purified water. The gel is filled in aluminium tubes.

II.2 Drug Substance

Estriol has a monograph in the Ph Eur.

Estriol is a white or almost white, crystalline powder which is sparingly soluble in ethanol, and practically insoluble in water. The structure of estriol has been adequately proven and its physico-chemical properties sufficiently described. Relevant information on chirality is presented. The route of synthesis has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The active substance specification includes relevant tests and the limits for impurities/degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies under ICH conditions have been conducted and the data provided are sufficient to confirm the retest period.

II.3 Medicinal Product

Blissel vaginal gel is formulated using excipients described in the current Ph Eur, except for polycarbophil which is controlled according to an acceptable USP monograph. All raw materials used in the product are of vegetable origin.

The product development has taken into consideration the physico-chemical characteristics of the drug substance.

The manufacturing process has been sufficiently described and critical steps identified. Results from the process validation studies confirm that the process is under control and ensure both batch to batch reproducibility and compliance with the product specification.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies under ICH conditions have been performed and data presented support the shelf life claimed in the SPC, when stored below 25°C.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology

In support of the application, the Applicant has performed several pharmacodynamic studies aimed at characterization of efficacy and safety of gel formulations containing estriol as active compound.

Single dose vaginal administration of estriol gel formulations to the ovariectomized female rat, considered a relevant animal model for the proposed indication, demonstrated a dose-related systemic absorption of estriol.

Furthermore, dose-related trophic effects on vaginal epithelium were observed when administered *in vivo* following single dose administration.

Repeated intravaginal administration of 0.01 µg or 0.1 µg estriol produced similar trophic effects on vaginal epithelium as those of a reference formulation (Ovestinon® 0.1%) containing a higher amount of estriol. The results thus indicate that in the ovariectomized rat, the efficacy of estriol can be of the same magnitude although the concentrations of active compounds differ.

In another vaginal repeated dose studies it was demonstrated that estriol gels containing 0.0002%, 0.002% or 0.005% (the gel formulation proposed for marketing) induced a trophic effect on vaginal tissues without inducing any significant trophic effect on uterine tissues. In contrast, the reference formulation Ovestinon® 0.1%) induced trophic effects on both tissue types. From a safety perspective this information is only considered supportive since although the ovariectomized female rat is considered a relevant animal model, there is a large difference between rats and women when it comes to hormone regulation in the reproductive system.

To conclude, in the ovariectomized female rat, local vaginal administration of estriol is absorbed systemically in a dose-related manner. Furthermore, a dose-related trophic effect of estriol on vaginal epithelium was observed, while no trophic effect of the formulation proposed for marketing was observed on uterine tissues.

III.2 Pharmacokinetics

Estriol is quickly absorbed following intravaginal administration to rats with T_{max} of 30 min. The duration of effect is approximately 8 hours. No accumulation of estriol in plasma has been observed following repeated treatment. Furthermore, no accumulation was noted in rat uterine tissue following repeated intravaginal treatment. The excretion of estriol is, similar to the metabolism, complex and different in different species including humans.

III.3 Toxicology

The toxicological profile of estrogens, of which estriol is an example, are by the assessor considered well known. However, the applicant has in support of the application submitted a literature overview of toxicity studies with estriol, which are briefly summarised and assessed below.

Three-months repeated dose toxicity studies demonstrated well known toxic effects of estriol mediated via the estrogenic action of the compound. No toxicokinetic data are available which can be accepted considering the well known toxicological properties of estriol and the proposed lower dose of the compound in the proposed formulation compared to already marketed products.

There are several publications on the genotoxic potential of estriol and other estrogens (reference to the nonclinical overview and summaries). The majority of these publications are old and the GLP status is uncertain. A chromosomal aberration study is according to existing guidelines missing. However, this can be accepted considering the long clinical experience with estriol and the proposed lower dose of estriol in the formulation proposed for marketing.

There are also several publications and overviews on the carcinogenic potential of estriol and other estrogens (reference to the the nonclinical overview and summaries). There is a relationship between estrogens and tumour development both in animals and humans. Concerning estrogen treatment in humans, there is a vast majority recommending treatment with lowest effective dose for as short time as possible. There is no concern for human safety with Blissel treatment considering the long clinical experience with vaginal estrogen treatment and the proposed lower dose of estriol in Blissel gel.

Local tolerance studies have been performed with the formulation proposed for marketing, 0.005% of estriol in a gel formulation. No vaginal irritation was demonstrated following 5 days of treatment of female rabbits. Although this study is short considering that the guideline on local tolerance recommends a 4-week study, it can however be accepted if adequate safety information can be obtained from the clinical studies.

No skin sensitization potential was observed with either formulation following 14 days of treatment of guinea-pig skin.

III.4 Ecotoxicity/environmental risk assessment

The Applicants view that no additional environmental risk assessment is necessary for the product Blissel is endorsed considering that estriol is a well known active substance and that the concentration of estriol is lower than in other approved products.

III.5 Discussion on the non-clinical aspects

The nonclinical documentation submitted in support of the application has some shortcomings. These can however be accepted considering the proposed lower dose of estriol in Blissel and the extensive clinical experience with vaginal administration of estriol. There is no concern for human safety with Blissel treatment from a nonclinical point of view.

IV. CLINICAL ASPECTS

IV.1 Introduction

This is a vaginal gel formulation for the treatment of vaginal atrophy, which contains a very low dose of estriol 0.005% (50 µg/g) per application.

IV.2 Pharmacokinetics

The pharmacokinetic information for this locally acting product can solely be used in the safety evaluation, *i.e.* to ensure that systemic exposure is low in comparison with other available formulation, but from an efficacy point of view, pharmacokinetics is not helpful. The Applicant has in support of this application submitted one pharmacokinetic study (ITFE 2026-C1) in which two strengths of the vaginal gel are compared with the marketed product Ovestinon following once daily application for 21 days. In addition, published data on general estriol pharmacokinetic characteristics have been submitted.

The systemic exposure of the Blissel vaginal gel formulations was approximately dose proportional following a single dose. The exposure decreases over time due to maturation of the vaginal epithelium, resulting in a lower absorption, a phenomenon which has been

observed previously with other formulations. The systemic exposure of the intended formulation Blissel vaginal gel 50 µg/g is considerably lower than for the marketed product Ovestinon vaginal cream, both after single and multiple dose administration, being almost negligible after repeated administration.

Following oral administration estriol is almost completely conjugated in the intestine to glucuronides (80~90%) and sulfates (10-20%). The glucuronides are rapidly excreted in the urine while sulphates can be measured in the blood. When administered vaginally there is less metabolism of estriol and the levels of unconjugated estriol were higher after vaginal than after oral administration. The terminal half-life following a single vaginal dose is short, approximately 1.5-3 hours. There are no studies of the pharmacokinetic behaviour in special populations (impaired organ function, elderly) and no information concerning drug-drug interactions. This lack of information is considered acceptable as the dose administered and the systemic exposure is low.

In summary, the pharmacokinetic documentation is considered sufficient for a safety assessment. There are no safety concerns given the systemic exposure.

IV.3 Pharmacodynamics

In Study ITFE-2026-C1, the Blissel vaginal gel 50 µg/g and marketed product Ovestinon showed no cases of atrophic cytological pattern at day 22. A reduced frequency of atrophic tissue and increase in frequency of slightly proliferative to highly proliferative tissue was observed for the three oestrogen formulations.

The vaginal cytological smears showed a marked improvement of the mean Maturation Index and change from baseline in Maturation Value (MV) on day 22 in the three groups of post-menopausal women who received the active treatments.

IV.4 Clinical efficacy

The Applicant has in support of this application submitted one randomized, double blind placebo controlled study (ITFE-2026-C2) to test the efficacy and safety of the new low concentration 0.005% estriol formulation on signs and symptoms of vaginal atrophy. Inclusion criteria were sufficient to enrol postmenopausal patients with objectively verified cytological vaginal atrophy, corresponding to the primary endpoint.

The primary endpoint, the change in maturation value (MV) after 12 weeks, reflects the effect on the vaginal mucosa and, therefore, MV could be considered a surrogate endpoint. The MV increased significantly ($p < 0.001$) versus placebo in the Blissel group already after 3 weeks and the difference remained throughout the study duration of 12 weeks. A significant decrease versus placebo in vaginal pH was observed for the Blissel. The mean and median pH was 5.1 and 5.0 respectively in the estriol group after 12 weeks of treatment with Blissel.

Among the secondary endpoints, vaginal dryness was the only symptom that all patients in the study reported at baseline. At baseline, 90% of patients reported dyspareunia, 50% complained of vaginal pruritus/itching, 40% of burning and 25% reported dysuria.

Vaginal dryness was the main secondary endpoint where significant efficacy was shown in comparison with placebo. After 12 weeks, 88 versus 67% ($p < 0.001$) were responders (i.e. reported improvement) with regard to vaginal dryness. It would be expected that vaginal dryness as a symptom is strongly associated with dyspareunia. However, there was no statistically significant difference at week 12 between Blissel and placebo with regard to responder rate for dyspareunia. This may reflect that some women may prefer to report vaginal dryness rather than disclosing sexual problems. Also, this parameter was a secondary endpoint,

so it was not considered for sample size estimation, and the study was not powered for a discriminatory analysis of this parameter.

After 12 weeks, the efficacy of Blissel for the treatment of postmenopausal atrophy was additionally shown by the statistically significant improvement evidenced by the investigators of the most outstanding signs indicative of vaginal atrophy, such as flattening of folds, pallor and fragility of the vaginal mucosa. The effect of Blissel on some of these signs and symptoms of vaginal atrophy became evident already after 3 weeks of treatment.

The patients in the Blissel group rated the effectiveness of the treatment as excellent or good in 74% compared to 43% in the placebo group. In the post-hoc analysis of the Global Symptom Score in the women treated with Blissel showed a change of 4.44 compared to 3.37 in the placebo group ($p=0.0187$).

In conclusion, the study provides some evidence for a clinical effect over placebo on vaginal dryness. As vaginal dryness was the most frequently reported most bothersome symptom, Blissel can be considered providing relief on a clinically relevant symptom.

IV.5 Clinical safety

Safety data with regard to potential systemic effects of vaginally applied Blissel product is limited. In the study ITFE-2026-C2 physical, gynaecological and transvaginal ultrasound examinations were performed in women treated with Blissel 50 µg estrogen for 12 weeks.

Together with the PK data, it could be concluded that the systemic effects of Blissel 50 µg are negligible and no systemic progestagens are needed. No AE related to breast or endometrium was observed in the Blissel treated group. It is not expected that this low dose would affect the endometrium after 12 weeks of treatment.

Local vulvovaginal pruritus and generalised pruritus were observed both in the active treatment group and placebo in study ITFE-2026-C2. However it was more frequently observed in the Blissel group than in placebo. In the study ITFE-2026-C1 it was more frequently observed in the reference group with Ovestinon.

To conclude, the clinical documentation submitted in support of the application can be accepted considering the proposed lower dose of estriol in Blissel and the extensive clinical experience with vaginal administration of estriol.

The observation of pruritus is in agreement with the tolerability profile described for other oestrogenic, intravaginal products, most of them with higher doses of oestrogen. It cannot be excluded that the vehicle might cause pruritus, but the frequency is similar to that reported for other vaginal products. The applicant also refers to 10 relevant references. Based on the figures of AEs and the referred studies the risk associated with the product is considered low.

IV.6 Discussion on the clinical aspects

Efficacy of Blissel 50 µg compared with placebo was demonstrated for vaginal dryness, MV, vaginal pH and flattening of folds, pallor and fragility of the vaginal mucosa after 12 week treatment. In women suffering of vaginal dryness as the most bothersome symptom there was also a significant difference between Blissel and placebo at the end of treatment. Blissel can be considered providing relief to women suffering from vaginal dryness.

V. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

User consultation

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The risk/benefit ratio is considered positive and Blissel, vaginal gel, 50 microgram/g is recommended for treatment of vaginal dryness in postmenopausal women.

VI. APPROVAL

The Decentralised procedure for Blissel, vaginal gel, 50 microgram/g was successfully finalised on 2010-07-28.

Public Assessment Report – Update

Scope	Procedure number	Product Information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached
						Y/N (version)