

Public Assessment Report

Scientific discussion

Progesteron GLF 100 mg and 200 mg soft capsules

(progesterone)

NL/H/3415/001-002/DC

Date: 6 June 2017

This module reflects the scientific discussion for the approval of Progesteron GLF 100 mg and 200 mg soft capsules. The procedure was finalised on 16 March 2016. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Progesteron GLF 100 mg and 200 mg soft capsules, from Goodlife Fertility BV.

The product is indicated for:

Gynaecological:

- Cycle disorders due to progesterone insufficiency, particularly:
 - Menstrual irregularities,
- Adjunctive use in hormone therapy with an oestrogen in menopausal women with an intact uterus.

The product is indicated for adults.

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Utrogestan, capsules 100 mg and 200 mg which has been registered in Belgium by Besins Healthcare Benelux since respectively 1 September 1981 and 9 January 2006. The MAH included a statement declaring that Progesteron GLF soft capsules are qualitatively and quantitatively identical to Utrogestan capsules.

The concerned member states (CMS) involved in this procedure were Belgium, Germany, Luxembourg and Poland.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Progesteron GLF 100 mg is a round, slightly yellow capsule and contains 100 mg progesterone (micronized). Progesteron GLF 200 mg is a ovoid, slightly yellow capsule and contains 200 mg progesterone (micronized).

The capsules are packed in PVC/Aluminium blisters.

The excipients are:

capsule content – sunflower oil and soya lecithin.

capsule shell – gelatin, glycerol, titanium dioxide (E171).

The content of the capsules is dose proportional.

II.2 Drug Substance

The active substance is progesterone (micronized), an established active substance described in the European Pharmacopoeia (Ph.Eur.). The substance is a white or almost white, crystalline powder or colourless crystals. It is practically insoluble in water, freely soluble in anhydrous ethanol, sparingly soluble in acetone and in fatty oils. The substance shows polymorphism and the stable α -form is produced consistently.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general

monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. with additional requirements for particle size distribution. Batch analytical data demonstrating compliance with this specification have been provided for three production scaled batches.

Stability of drug substance

The active substance is stable for 3 years when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development

The MAH has declared that the drug products at issue are manufactured at the same manufacturing site, using the same ingredients (active substance source and excipients) and manufacturing process as the reference product Utrogestan soft capsules. A contract of comarketing has been signed between the innovator and the MAH of Progesteron GLF. Hence no pharmaceutical development studies or bioequivalence studies have been performed.

Manufacturing process

The manufacturing process is a well-established and conventional process for preparing soft capsule formulations and consists of preparation for capsule shell and content, encapsulation, capsule drying and packaging. The process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three full scaled batches in accordance with the relevant European guidelines.

Control of excipients

The excipients are controlled as per Ph. Eur. monographs. The specification of soya lecithin is according to the United States Pharmacopeia monograph. These specifications are acceptable.

Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identity, assay, related substances, uniformity of dosage units, disintegration, average mass of filled capsules, uniformity of capsule mass, particle size of progesterone and microbial purity. The release and shelf-life requirements are identical except for related substances which are not tested at release and the uniformity of dosage units which is not tested throughout shelf-life. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data on three full scaled batches of each strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for two full scale batches and one pilot scaled batch of each strength stored at 25°C/60% RH (24 months), 30°C/65% RH (24 months), 30°C/75% RH (24 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed packaging. Some changes were observed in assay value at long-term, intermediate and accelerated conditions. A photostability study has been performed, showing that the capsules do not have to be protected from light. The proposed shelf-life of 36 months and storage condition 'store below 30°C, do not refrigerate' are justified.

Specific measures for the prevention of the transmission of animal spongiform encephalopathies
 Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies: a certificate of suitability issued by the EDQM has been provided for the excipient gelatine.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Progesteron GLF has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Progesteron GLF is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a generic formulation of Utrogestan which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Progesterone is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

Biowaiver

No bioequivalence study was performed for this application. The generic drug product is going to be manufactured by the same manufacturer and site as the reference product. Furthermore, the generic drug product has the same ingredients and same manufacturing process. A declaration from the manufacturing site certifying that both drug products are manufactured identically was provided. Therefore, no further bioequivalence study is considered necessary and bioequivalence can be sufficiently assumed.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Progesteron GLF.

- Summary table of safety concerns as approved in RMP

Important identified risks	<ul style="list-style-type: none"> - Use in severe liver dysfunction - Use in patient with liver tumours
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	<ul style="list-style-type: none"> - Suspected or confirmed breast or genital organ neoplasia - Thromboembolic diseases, active or in the history - Use in cerebral haemorrhage - Use in undiagnosed genital bleeding - Use in porphyria
Important potential risks	- Impairment to glucose tolerance
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Utrogestan. No new clinical studies were conducted. A bioequivalence study was not deemed necessary, as the products at issue and the reference products are identical in qualitative and quantitative composition.. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. 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 test consisted of two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. 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.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Progesteron GLF 100 mg and 200 mg soft capsules have a proven chemical-pharmaceutical quality and are generic forms of Utrogestan 100 mg and 200 mg capsules. Utrogestan is a well-known medicinal product with an established favourable efficacy and safety profile.

The MAH did not submit a bioequivalence study, but provided sufficient information to demonstrate that the product has the same quantitative and qualitative composition as Utrogestan and is produced at the same manufacturing site.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Progesteron GLF with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 16 March 2016.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Change in the (invented) name of the medicinal product; for Nationally Authorised Products (Germany)	NL/H/3415/1-2/IB/001	IB	14-10-2016	22-11-2016	Approved	N
Change in the (invented) name of the medicinal product; for Nationally Authorised Products (Poland)	NL/H/3415/1-2/IB/002	IB	30-11-2016	17-02-2017	Approved	N
Change in the (invented) name of the medicinal product; for Nationally Authorised Products (Belgium and Luxembourg)	NL/H/3415/IB/003/G	IB	30-01-2017	01-03-2017	Approved	N
Introduction of, or changes to, a summary of pharmacovigilance system for medicinal products for human use; Introduction of, or changes to, a summary of pharmacovigilance system for medicinal products for human use	NL/H/3415/IA/004/G	IA	16-03-2017	03-04-2017	Approved	N