COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Femke 30 mg, film-coated tablets

(ulipristal acetate)

NL/H/4223/001/DC

Date: 4 April 2019

This module reflects the scientific discussion for the approval of Femke 30 mg, film-coated tablets. The procedure was finalised at 3 January 2019. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
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 Femke 30 mg, film-coated tablets, from Mylan B.V.

The product is indicated for emergency contraception within 120 hours (5 days) of unprotected sexual intercourse or contraceptive failure.

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 EllaOne, 30 mg tablets (EU/1/09/522) which has been registered in the EEA by Laboratoire HRA Pharma since 15 May 2009 through a centralised procedure.

The concerned member states (CMS) involved in this procedure were Austria, Czech Republic, Germany, Denmark, Finland, Italy, Norway, Poland, Portugal, Romania and Sweden.

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

II. QUALITY ASPECTS

II.1 Introduction

Femke is a white, round, biconvex, film-coated tablet. Each tablet contains 30 mg ulipristal acetate.

The film-coated tablets are packed in PVC-PVDC-Aluminium blisters.

The excipients are:
Tablet core - lactose monohydrate, pregelatinised starch (maize), sodium starch glycolate and magnesium stearate
Coating - hypromellose (E464), hydroxypropylcellulose (E463), stearic acid (E570), talc (E553b) and titanium dioxide (E171)

II.2 Drug Substance

The active substance is ulipristal acetate, an established substance, however not described in the European Pharmacopoeia (Ph.Eur.). It is a white to yellow solid with pH dependent solubility in water at 37°C (23 mg/mL at pH 1 and down to 5 µg/mL at pH 6.8). It has five asymmetric carbons and shows specific optical rotation. Ulipristal acetate is known to exhibit

polymorphism. Two drug substance suppliers are used. Manufacturer one produces polymorph Form A and manufacturer two produces polymorph Form B.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

Manufacturer one - The manufacturing process involves four stages. The drug substance is sufficiently characterised with regard to the chemical structure. The intended polymorphic form (Form A) is consistently manufactured. The stereomeric purity of a starting material and the stereomeric purity of an intermediate of the synthesis are adequately controlled by suitable analytical controls.

Manufacturer two – The manufacturing process involves five steps. The drug substance is sufficiently characterized with regard to the chemical structure. The intended polymorphic form (Form B) is consistently manufactured.

Quality control of drug substance

The active substance specification is considered adequate to control the quality. A compiled specification covering the tests applied for the active substance from both suppliers is provided. Descriptions of analytical methods and validations have been provided. One method and one set of limits are applied for the particle size distribution control of active substance from both suppliers. Batch analytical data demonstrating compliance with this specification have been provided for a total of three batches.

Stability of drug substance

Manufacturer one - Stability data have been provided for three batches stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). The provided stability data support the proposed re-test period of 48 months.

Manufacturer two - Stability data have been provided for three batches stored at 25°C/60% RH (12 months) and 40°C/75% RH (6 months). The provided stability data support the proposed re-test period of 12 months.

II.3 Medicinal Product

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The choice of excipients is

justified and their functions explained. The proposed packaging and manufacturing process are acceptable.
The batch used in the bioequivalence study was manufactured according to the proposed manufacturing process with drug substance manufactured by manufacturer one. The products used in the bioequivalence study are acceptable. Dissolution results have been provided that confirm that the difference in polymorphic form (Form A versus Form B) has no impact on the quality of the drug product.

Manufacturing process
The manufacturing process consists of dispensing, blending, granulation, sieving, lubrication, compression, and film-coating and has been validated according to relevant European guidelines. The film-coated tablets are prepared by wet granulation and compression. It is considered a standard manufacturing process. Process validation data on the product have been presented for four batches in accordance with the relevant European guidelines.

Control of excipients
The excipients comply with the Ph.Eur., except for the film-coating excipients. Functional characteristics have been included where relevant. For the film-coating, in house specification has been provided. 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, identification, uniformity of dosage units by content uniformity, dissolution, assay, related substances and microbiological quality. 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 from three batches of the drug product manufactured with drug substance from manufacturer one and one batch manufactured with drug substance from manufacturer two 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 four batches stored at 25°C/60% RH (12 months) and at 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The results of the photostability study showed that the tablets are sensitive for light but not if stored in the blister packaging. On basis of the data submitted, a shelf life was granted of 18 months, stored in the original package in order to protect from light and without temperature storage conditions.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
None of the materials used in the manufacture of the Ulipristal acetate film-coated tablets, except lactose monohydrate, are of animal or human origin. TSE-BSE certificates of all the raw materials, including lactose monohydrate, used in the manufacturing have been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Femke has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. The following post-approval commitments were made:

- The MAH has committed to implement a pregnancy registry before placing the product on the market.
- The MAH has committed to submit a study protocol for the pregnancy registry within 3 months after finalisation of the procedure. Together with this, a synopsis of the pregnancy registry will be included in the RMP.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Femke 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 EllaOne 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

Ulipristal acetate 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.

For this generic application, the MAH has submitted a bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Femke 30 mg, film-coated tablets (Mylan B.V., NL) is compared with the pharmacokinetic profile of the reference product EllaOne, 30 mg tablets (Laboratoire HRA Pharma, France).

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of the EU reference product. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 42 healthy female subjects, aged 19-80 years. Each subject received a single dose (30 mg) of one of the 2 ulipristal acetate formulations. The tablet was orally administered with water after an overnight fast for at least 10 hours. There were 2 dosing periods, separated by a washout period of 21 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 6, 8, 14, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable.

Ulipristal acetate may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption. Therefore, a food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

Analytical/statistical methods

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results

Two subjects were withdrawn from the study due to adverse events (diarrhoea and Meniere's disease) prior to the second period. Therefore, a total of 40 subjects completed the study were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of ulipristal acetate under fasted conditions.

Treatment N=40	**AUC_{0-72} (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**

Test	629.67 ± 50.21	230.15 ± 53.21	0.75 (0.50 – 4.00)
Reference	634.58 ± 53.33	236.53 ± 49.54	0.75 (0.50 – 6.00)
***Ratio (90% CI)**	1.02 (0.95 – 1.09)	0.94 (0.84 – 1.05)	
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity **AUC_{0-t}** area under the plasma concentration-time curve from time zero to t hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum concentration			

**In-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Femke is considered bioequivalent with EllaOne.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

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 Femke.

Table 2. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	- Effects on pregnancy maintenance/off label use - Risk of incomplete abortion and heavy bleeding - Effects on foetus and new-borns - Risk of ectopic pregnancy - Concomitant use of CYP3A4 inducers - Liver effects - Delayed menstrual period >60 days / amenorrhea - Ovarian cysts
Missing information	- Effect of concomitant use of progestin-only contraception - Effect in patients with severe asthma treated by oral glucocorticoid - Effects in women with impaired liver function

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 EllaOne. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) 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: a pilot test with 2 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.
The results show that the PL 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

Femke 30 mg, film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of EllaOne, 30 mg tablets. EllaOne is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

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 Femke with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 3 January 2019.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse