COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Ecinq 30 mg film-coated tablets (ulipristal acetate)

NL/H/5170/001/MR

Date: 6 February 2023

This module reflects the scientific discussion for the approval of Ecinq 30 mg film-coated tablets. The procedure was finalised at 8 April 2021. 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
MRP	Mutual recognition procedure
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 Ecinq 30 mg tablets, from Aspen Healthcare Malta Limited.

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 mutual recognition procedure (MRP) concerns a generic application claiming essential similarity with the innovator product ellaOne, 30 mg tablets which has been registered in the EU via a centralised procedure by Laboratoire HRA Pharma since 15 May 2009 (EU/1/09/522).

The concerned member state (CMS) involved in this MRP procedure was Malta.

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

II. QUALITY ASPECTS

II.1 Introduction

Ecinq is a white, round and biconvex film-coated tablet that is embossed with *"U30"* on one side. Ecinq contains as active substance 30 mg ulipristal acetate. The film-coated tablets are packed in transparent PVC/PVDC-aluminium blisters.

The excipients are:
Tablet core - lactose monohydrate, pre-gelatinised starch (maize), sodium starch glycolate and magnesium stearate.
Tablet coating - hypromellose (E464), hydroxypropyl cellulose (E463), stearic acid (E570), talc (E553b) and titanium dioxide (E171).

II.2 Drug Substance

The active substance is ulipristal acetate, which is a white to yellow solid with pH dependent solubility in water at 37°C. It has five asymmetric carbons and shows specific optical rotation. Ulipristal acetate is known to exhibit polymorphism. The active substance is produced by two manufacturers.

For both manufacturers of ulipristal acetate, the Active Substance Master File (ASMF) procedure is used. 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 I

The first manufacturer produces polymorphic form I of the active substance. The manufacturing process consists of four stages. Via different reactions, including oxidation, synthesis, isolation, hydrolysation and crystallisation, the final form I is yielded. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised.

Manufacturer II

The second manufacturer produces polymorphic form II of the active substance. The manufacturing process consists of five stages. Via different reactions, including epoxidation, purification and micronisation, the final form II is yielded. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised.

Quality control of drug substance

A compiled specification covering the tests applied for the active substance from both suppliers is provided. Analytical methods and validations have been described. One method and one set of limits are applied for the particle size distribution control of the active substance from both manufacturers. The active substance specifications are considered adequate to control the quality and meet in-house criteria and requirements of the monograph in the European Pharmacopoeia (Ph.Eur.). Batch analytical data demonstrating compliance with this specification have been provided for two batches per manufacturer.

Stability of drug substance

Stability data on the active substance have been provided for three batches per manufacturer in accordance with applicable European guidelines, demonstrating the stability of the active substance up to 48 months (manufacturer I) and up to 24 months (manufacturer II). Based on the data submitted, for manufacturer I a retest period could be granted of 48 months when stored in stated conditions. For manufacturer II, a retest period could be granted of 12 months when stored in stated conditions.

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. A bioequivalence study has been performed, which will be discussed in section IV. Dissolution results have been provided that confirm that the difference in polymorphic form (form I versus form II) has no impact on the quality of the drug product.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for four batches in accordance with the relevant European guidelines. The manufacturing process consists of several steps, including dispensing, blending, granulation, sieving, lubricating, compressing, and film-coating.

Control of excipients

The excipients, except the coating (AquaPolish white), comply with the Ph. Eur. Functional characteristics have been included where relevant. For the coating, in-house specifications have 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 four batches from the proposed production site have been provided. Three batches were produced with the active substance from manufacturer I, one batch was produced with the active substance from manufacturer II. The batch analytical data are in compliance with the specification.

Stability of drug product

Stability data on the product have been provided for four batches in accordance with applicable European guidelines demonstrating the stability of the product for 24 months at 25°C/60% RH, and for six months at 40°C/75% RH. A photostability study was conducted which showed sensitivity for light, but not if stored in the blister packaging. On basis of the data submitted, a shelf life was granted of 24 months. No specific temperature storage conditions need to be included in the SmPC or on the label.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Certificates of suitability issued by the EDQM for lactose monohydrate and other raw materials have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Ecinq 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 Ecinq 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 Ecinq 30 mg film-coated tablets (Aspen Healthcare Malta Limited, Malta) 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 a comparison of dissolution results and compositions with the reference product. The formula and preparation of the bioequivalence batch are identical to the formula proposed for marketing.

Bioequivalence study

Design

A single-dose, randomised, open-label, two-period, two-sequence, two-treatment, single-centre, two-way crossover bioequivalence study was carried out under fasted conditions in 42 healthy female subjects, aged 18 years and older. Each subject received a single dose (30 mg) of one of the two ulipristal acetate formulations. The tablet was orally administered with 240 ml water after a fasting period of at least ten hours. There were two 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.

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 withdrew from the study due to adverse events. This left 40 subjects 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_{0-72} area under the plasma concentration-time curve from time zero to 72 hours
C_{max} maximum plasma concentration
t_{max} time for maximum concentration

**ln-transformed values*

Conclusion on bioequivalence study

The 90% confidence intervals calculated for AUC_{0-72} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study, Ecinq 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 Ecinq.

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 risk minimisation measures are sufficient for the risks and areas of missing information. A joint post-authorization safety study (PASS) is performed by MAHs of generic ulipristal acetate 30 mg products, to assess clinical follow-up and outcomes of pregnancies exposed to the product. This is run via a pregnancy exposure registry, aimed primarily at collecting all data about pregnancy outcome in women exposed to ulipristal acetate (30 mg) for any reason, with a secondary objective to monitor the important identified risks related to pregnancy (the top four listed in the table above).

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 language used for the purpose of user testing the PL was English. The test consisted of a pilot test with two participants, followed by two rounds with ten 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

Ecinq 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 Ecinq with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finalised with a positive outcome on 8 April 2021.

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
NL/H/5170/001/IA/001	MAH address change	Yes	12-9-2021	Approved	N/A
NL/H/5170/001/IA/002	Change(s) in the product information following the outcome of a PSUR – Implementation of wording agreed by the competent authority	Yes	13-4-2022	Approved	N/A
NL/H/5170/001/IA/003	MAH address change	Yes	31-1-2023	Approved	N/A