CBG MEB

Public Assessment Report

Scientific discussion

Entecavir Polpharma 0.5 mg and 1 mg, film-coated tablets

(entecavir monohydrate)

NL/H/3819/001-002/DC

Date: 14 November 2017

This module reflects the scientific discussion for the approval of Entecavir Polpharma 0.5 mg and 1 mg, film-coated tablets. The procedure was finalised on 17 May 2017. 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
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 Entecavir Polpharma 0.5 mg and 1 mg, film-coated tablets from Pharmaceutical Works Polpharma S.A.

The product is indicated for the treatment of chronic hepatitis B virus (HBV) infection in adults with:
- compensated liver disease and evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis
- decompensated liver disease

For both compensated and decompensated liver disease, this indication is based on clinical trial data in nucleoside naive patients with HBeAg positive and HBeAg negative HBV infection.

Paediatric population
Treatment of chronic HBV infection in nucleoside naive paediatric patients from 2 to 18 years of age with compensated liver disease who have evidence of active viral replication and persistently elevated 2 serum ALT levels, or histological evidence of moderate to severe inflammation and/or fibrosis.

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 Baraclude 0.5 mg and 1 mg, film-coated tablets which has been registered in the EEA by Bristol-Myers Squibb Pharma EEIG through centralised procedure (EU/1/06/343/001-007) since 26 June 2006.

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

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

II. QUALITY ASPECTS

II.1 Introduction

Entecavir Polpharma is a film-coated tablet:
The 0.5 mg strength is a white, oval shaped tablet with break line on both sides. The tablet can be divided into equal doses.
The 1 mg strength is a pink, oval shaped tablet with break line on both sides. The tablet can be divided into equal doses.

Each tablet contains as active substance 0.5 mg or 1 mg entecavir, as monohydrate.

The film-coated tablet are packed in OPA/Aluminium/PVC blisters.

The excipients are:
Tablet core - microcrystalline cellulose, lactose monohydrate, pregelatinised starch, crospovidone type A and magnesium stearate.
Film-coating - titanium dioxide (E171), macrogol, polysorbate 80, hypromellose 6 mPas (cP), hypromellose 3 mPas (cP) (only 0.5 mg tablets) and red iron oxide (E172) (only 1 mg tablets).

The two tablet strengths are dose proportional.

II.2 Drug Substance

The active substance is entecavir monohydrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Entecavir monohydrate is a white or almost white powder. It is practically insoluble in water, anhydrous ethanol and heptane and slightly soluble in methanol. The Ph.Eur. monograph does report the existence of polymorphism (anhydrous and monohydrate). Entecavir monohydrate is consistently manufactured for this procedure.

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
The manufacturing process of entecavir monohydrate consists of seven steps followed by recrystallization. The proposed starting materials are acceptable. The active substance has been adequately characterised and acceptable specifications have been adopted for the solvents and reagents.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. The MAH adopted the specification of the ASMF-holder as drug substance specification, with an additional limit for particle size distribution, which was set experimentally. The proposed limits for particle size distribution are acceptable. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
Stability data on the active substance have been provided for three batches in accordance with applicable European guidelines demonstrating the stability of the active substance for 33 months. Based on the data submitted, a retest period could be granted of 36 months when stored under the 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 are explained. The same excipients as in the reference product were selected, except for povidone which was replaced with pregelatinised starch for stability reasons. The main development studies performed were the characterisation of the reference product, Quality Target Product Profile (QTPP) of the drug product, excipient compatibility studies, prototype formulation and optimisation studies. Risk assessments have been performed at various stages. The MAH justified the break line on the tablets, which is not present on the innovator product. It has been demonstrated that the break line is functional and that the tablets can be divided into equal tablet halves of 0.25 mg and 0.5 mg.

A bioequivalence study has been performed with the 1 mg product strength. The provided dissolution profiles of the test and the reference product batches at three different pH and in the medium proposed for routine dissolution testing, support bioequivalence. For the 0.5 mg product strength, a biowaiver of strengths has been justified based on the results of *in vitro* dissolution studies. In all cases the tablets were dissolved for more than 85% in 15 minutes. The pharmaceutical development has been adequately performed.

Manufacturing process
The manufacturing process consists of premixture preparations, powder mixture preparation, (wet) granulation, drying, sieving, blending, compression, coating and packaging. The process is considered to be a non-standard manufacturing process. The manufacturing process has been adequately

validated according to relevant European guidelines. Process validation of the drug product has been presented for three full scale commercial batches of both strengths. The drug product is manufactured at two manufacturing sites by a similar manufacturing process.

Control of excipients
With the exception of the two Opadry film-coatings, all excipients comply with their respective Ph.Eur. monograph. For the Opadry film coatings, an in-house specification is included. 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, disintegration, dissolution, water content, related substances, assay and microbial 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 commercial scale from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the drug product has been provided for three full scale batches of each tablet strength per manufacturer.

Manufacturer-I
The drug product was stored up to eighteen months at 25°C/60% RH and at 30°C/65% RH, and for six months at 40°C/75% RH. All batches comply with the specifications.

Manufacturer-II
The drug product was stored for up to nine months at 25°C/60% RH and for six months at 40°C/75% RH. All batches comply with the specification.

The drug product was shown to be photostable, as no significant changes were observed in the photostability studies.

On the basis of the available stability data, the proposed shelf-life of 24 months with the storage condition ‘Do not store above 30ºC. Store in the original package.’ can be granted.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
The drug substance and all excipients used, other than lactose monohydrate, are from non-animal and non-human origin. Scientific data and/or certificates of suitability issued by the EDQM 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 Entecavir Polpharma 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 Entecavir Polpharma 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 Baraclude 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

Entecavir monohydrate 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 one bioequivalence study, which is discussed below.

IV.2 Pharmacokinetics

Bioequivalence study
The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Entecavir Polpharma 1 mg, film-coated tablets (Polpharma Pharmaceutical Works, Poland) is compared with the pharmacokinetic profile of the reference product Baraclude 1 mg film-coated tablets (Bristol-Myers Squibb Pharma, Germany).

The choice of the reference product
The choice of the reference product in the bioequivalence study has been justified. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

Biowaiver
A biowaiver to the 0.5 mg tablet is acceptable as all the criteria for biowaiver are met:
- The two strengths are manufactured by the same manufacturer and manufacturing process.
- The two strengths are dose-proportional.
- Oral entecavir shows linear pharmacokinetics over the dose range of 0.1 – 1.0 mg/day
- Dissolution for both strengths is very rapid (≥95% within 5 minutes) at all three pH's (pH 1.0, 4.5 and 6.8)

Design
A single center, randomised, single dose, laboratory blinded, two period, two sequence, crossover bioequivalence study was carried out under fasted conditions in 26 healthy male and female subjects, aged 18-55 years. Each subject received a single dose (1 mg) of one of the two entecavir monohydrate formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. There were two dosing periods, separated by a washout period of 28 days.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.5, 0.67, 0.83, 1.0, 1.25, 1.5, 1.75, 2.0, 3.0, 4.0, 6.0, 9.0, 12.0, 16.0, 24.0, 36.0, 48.0 and 72.0 hours after administration of the products.

The design of the study is acceptable. The fasting conditions are in accordance with the product specific guidance.

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
One subject discontinued the study due to emesis within the restriction period Therefore, 25 subjects were eligible for pharmacokinetic analysis.

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

Treatment N=25	**AUC_{0-t}** pg.h/ml	**C_{max}** pg/ml	**t_{max}** h
Test	31939.6 ± 43	10955.5 ± 20	0.83 (0.50 – 1.50)
Reference	32198.6 ± 43	10826.4 ± 22	0.83 (0.50 – 1.50)
***Ratio (90% CI)**	0.99 (0.97 – 1.01)	1.02 (0.95 – 1.09)	--

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

**ln-transformed values*

Conclusion on bioequivalence study
The 90% confidence intervals calculated for AUC_{0-t} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Entecavir Polpharma 1 mg, film-coated tablets is considered bioequivalent with Baraclude 1 mg film-coated tablets.

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 Entecavir Polpharma.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Exacerbation of hepatitis • Entecavir resistance • Emergence of resistant HIV in HIV/HBV co-infected patients not concurrently receiving effective HIV treatment
Important potential risks	• Carcinogenicity • Mitochondrial toxicity
Missing information	• Long term safety and clinical outcomes data • Use in the paediatric population • Use in pregnancy and lactation • Use in elderly patients (≥65 years of age) • Use in severe acute exacerbation of chronic hepatitis B

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 Baraclude. 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

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Baraclude. The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Entecavir Polpharma 0.5 mg and 1 mg, film-coated tablets has a proven chemical-pharmaceutical quality and is a generic form of Baraclude 0.5 mg and 1 mg film-coated tablets. Baraclude 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 Entecavir Polpharma with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 17 May 2017.

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