CBG MEB

Public Assessment Report

Scientific discussion

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

(entecavir monohydrate)

NL/H/3830/001-002/DC

Date: 11 January 2018

This module reflects the scientific discussion for the approval of Entecavir CF 0.5 mg and 1 mg, film-coated tablets. The procedure was finalised on 20 April 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 CF 0.5 mg and 1 mg, film-coated tablets from Centrafarm B.V.

Adult population
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 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 states (CMS) involved in this procedure were Denmark, Spain, Finland, France, Poland, Sweden and Slovenia.

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

II. QUALITY ASPECTS

II.1 Introduction

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

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

The film-coated tablets are packed in Alu/Alu blisters.

The excipients are:
Tablet core - Microcrystalline cellulose, lactose monohydrate, maize starch pregelatinised, crospovidone (Type A) (E1202) and magnesium stearate
Tablet coating - Titanium dioxide (E171), hypromellose (E464), macrogol 400 and polysorbate 80. The 1 mg strength additionally contains red iron oxide.

The two tablet cores 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 white to off white powder. It is

practically insoluble in water, anhydrous ethanol and heptane and slightly soluble in methanol. Entecavir monohydrate possesses three chiral centres The Ph.Eur. monograph does report the existence of polymorphism (anhydrous and monohydrate), one form is consistently produced. For the current application the active substance is isolated in the monohydrate form.

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 consists of seven steps followed by recrystallisation. The drug substance 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 and meets the requirements of the monograph in the Ph.Eur. The MAH has adopted the specification of the ASMF-holder, with an additional limit for particle size distribution, which was set experimentally. The proposed limits for particle size distribution are considered to be acceptable. Batch analytical data demonstrating compliance with the previous drug substance specification and has been provided for 3 batches of the active substance.

Stability of drug substance
No data has been provided by the applicant on the stability of the drug substance. The MAH has confirmed that the same re-test period and storage conditions are used as are defined in the ASMF. The re-test period for the drug substance is 36 months if 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. 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 pharmaceutical development has been adequately performed.
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 pHs and in the medium proposed for routine dissolution testing (phosphate buffer pH 6.8), support bioequivalence. For the 0.5 mg product strength, a bio-waiver of strengths has been justified based on the results of *in vitro* dissolution studies.

Manufacturing process
The manufacturing process consists of premixture preparations, powder mixture preparation, blending, compression, coating and packaging. The process is considered to be a non-standard manufacturing process. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for 3 full scale batches of both strengths in accordance with the relevant European guidelines.

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. Functional-related characteristics, described in the Ph. Eur. monographs of microcrystalline cellulose, lactose monohydrate, pregelatinised starch, crospovidone and magnesium stearate, have been discussed and

additional tests for particle size distribution have been included into the excipient specifications of microcrystalline cellulose, lactose monohydrate and magnesium stearate.

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. The proposed release and shelf-life specification tests and limits are acceptable. 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 3 commercial scale batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the drug product have been provided for 3 full scale batches of each strength, stored at 25°C/60% RH (up to 18 months), 30°C/65% RH (up to 18 months) and 40°C/75% RH (6 months). The drug product was stored in bulk at 25°C/60% RH (12 months) and 40°C/75% RH (3 months).
When the drug product is stored under long term and intermediate conditions for eighteen months, the batches show a slight increase in water content (although it is noted that this increase is observed only in the first three months of storage). When the drug product is stored for six months under accelerated conditions, some trends and changes are seen. Therefore, a storage condition is added.
The drug product was shown to be photo stable, as no significant changes were observed in the tested parameters when the 0.5 mg tablets were directly exposed to UV and fluorescent light. The submitted stability data show only little changes over time in the obtained parameter results and normal analytical variability is observed.
No significant changes were observed in the tested parameters for the drug product stored in bulk, only some analytical variation is seen.
On the basis of the available stability data, the proposed shelf-life of 24 months (i.e. two years) with the storage condition 'Do not store above 30 ºC. Store in the original package.' can be granted.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
BSE/TSE declarations of the manufacturers of the excipients and the drug substance were provided. 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 CF 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 CF 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 CF 1 mg, film-coated tablets (Centrafarm B.V., The Netherlands) is compared with the pharmacokinetic profile of the reference product Baraclude 1 mg, film-coated tablets (Bristol-Myers Squibb GmbH & Co. KGaA, 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
The MAH was granted a biowaiver for the lower strength Entecavir CF 0.5 mg film-coated tablets based on the following arguments:

- The qualitative and quantitative composition of the different strengths is dose proportional and only differs in the film coating, which is acceptable and in accordance with the guideline.
- Both strengths of Entecavir CF are manufactured by the same process.
- Entecavir has linear pharmacokinetics over the therapeutic dose range.
- Both tablet strengths have comparable dissolution profiles according to the provided *in vitro* dissolution data.

Design
A single-centre, randomised, single-dose, open-label, two-way 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 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 study design is acceptable. The wash-out period of 28 days is long enough to prevent a carry over. Considering a terminal elimination half life of 128-149 hours, AUC truncated at 72 hrs is considered acceptable parameter for determination of the absorption phase of an immediate release product.

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 was withdrawn from the study due to emesis. Therefore, 25 subjects completed the study and 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_{0-72}** pg.h/ml	**C_{max}** pg/ml	**t_{max}** h
Test	31939.6 ± 4309.6	10955.5 ± 2047.0	0.83 (0.50 – 1.50)
Reference	32198.6 ± 4333.2	10826.4 ± 2243.5	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 CF is considered bioequivalent with Baraclude.

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 CF.

Summary table of safety concerns as approved in RMP:

Important identified risks	• Exacerbation of hepatitis • ETV 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

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: a pilot test with 3 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 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

Entecavir CF 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 CF with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 20 April 2017.

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/3830/IB/001/G	– Change in the (invented) name of the medicinal product; for Nationally Authorised Products – Introduction of, or changes to, a summary of pharmacovigilance system for medicinal products for human use	-	10-01-2018	Approved	-