CBG MEB

Public Assessment Report

Scientific discussion

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

(entecavir monohydrate)

NL/H/3973/001-002/DC

Date: 3 May 2018

This module reflects the scientific discussion for the approval of Entecavir Vocate 0.5 mg and 1 mg, film-coated tablets. The procedure was finalised on 14 February 2018. 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 Entecavir Vocate 0.5 mg and 1 mg, film-coated tablets, from Vocate Pharmaceuticals SA.

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 state (CMS) involved in this procedure was Greece.

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

II. QUALITY ASPECTS

II.1 Introduction

Entecavir Vocate is a triangle shaped biconvex film-coated tablet:
The 0.5 mg strength is a white to off white film-coated tablet debossed with ‘J' on one side and ‘110’ on the other side.
The 1 mg strength is a pink film-coated tablet debossed with 'J' on one side and '111' on the other side.

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 or high density polyethylene (HDPE) bottles with child resistant polypropylene closure containing 30 or 90 film-coated tablets and silica gel canister.

The excipients are:
Tablet core - calcium carbonate, pregelatinised starch, carmellose sodium, soy polysaccharides, citric acid monohydrate and sodium stearyl fumarate.
Tablet coating - hypromellose 6cP, titanium dioxide (E171), macrogol 400, polysorbate 80 (only 0.5 mg strength) and iron oxide red (E172) (only 1 mg strength).

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.). The active substance is a off-white to white coloured powder and is insoluble in water. Entecavir contains three stereogenic centres in its structure and is manufactured as the pure 1S,3R,4S enantiomer. Entecavir shows polymorphism and is consistently manufactured having the same polymorphic form that was demonstrated to remain stable during storage of the drug substance.

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 is described in six chemical transformation steps. No class 1 organic solvents are used in the manufacturing process. The active substance has been adequately characterised and acceptable specifications have been adopted for the starting materials, 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. It contains additional requirements for identity, polymorphic identity and residual solvents that have been adopted from the active substance manufacturer as well as additional requirements for microbiological quality and particle size distribution by the finished product manufacturer. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three full scaled batches.

Stability of drug substance

Stability data on the active substance have been provided for three full scaled batches stored at 25°C/60% RH (48 months) and 40°C/75% RH (6 months) and a fourth full scaled batch that was only stored at 40°C/75% RH (6 months). No clear trends or changes were seen at both storage conditions in the tested parameters. The drug substance was shown not to be light sensitive when exposed to ICH light conditions. Based on the data submitted, a retest period of 60 months with storage conditions 'Preserve in tight containers' and 'This drug substance does not require any special temperature storage conditions' could be granted.

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 main development studies performed were the characterisation of the reference products, development of the dissolution method, formulation optimisation studies and manufacturing process optimization studies. The choices of the packaging and manufacturing are considered justified.

A bioequivalence (BE) study has been performed with the 1 mg product strength. For the 0.5 mg product strength a biowaiver has been justified based on the results of in vitro dissolution studies. The test batch used in the BE study was manufactured according to the finalised composition and manufacturing process. Similarity in dissolution was shown for the 0.5 mg strength versus the BE study test batch in 0.1N HCl, pH 4.5 and pH 6.8 medium (>95% in 5 minutes). The pharmaceutical development of the product has been adequately performed.

Manufacturing process
The main steps of the manufacturing process are the dry mixing of intra granular components, wet granulation using a solution of active substance in water, mixing with extra granular components and lubrication, compression, film-coating and packaging. The manufacturing process has been validated according to relevant European guidelines. Process validation data on the product have been presented for three full scale batches in accordance with the relevant European guidelines.

Control of excipients
Except for the non-compendial soy polysaccharides and the film-coating mixtures, the excipients comply and are tested in accordance with their Ph.Eur. monographs. Soy polysaccharides and the film-coating mixtures are controlled according to their suppliers specifications. The 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 (also for the colorants), average mass, water content, dissolution, uniformity of dosage units, related substances, assay and microbiological examination. Except for water content and related substances, the release and shelf-life requirements are identical. 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 three full scaled batches 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 three full scaled batches per strength stored at 25°C/60% RH (18-36 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to ICH stability guidelines. The batches were stored in the blisters and the bottles. The stability data show an increase of impurities that was most pronounced at accelerated conditions. Dissolution seems to slightly decrease during storage of the drug product, mainly at accelerated conditions. No trends or changes were observed in any of the other tested parameters. The proposed shelf-life of 3 years without any special storage requirements is justified.

Stability data has been provided demonstrating that the product remains stable for 90 days following first opening of the HDPE container when stored at 25°C/60% RH and in-use conditions were simulated. No clear trends or changes were observed. No separate in-use shelf life was proposed for the product in the product information.

Specific measures for the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Entecavir Vocate 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 Vocate 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 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

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Entecavir Vocate 1 mg, film-coated tablets (Vocate Pharmaceuticals SA, Greece) is compared with the pharmacokinetic profile of the reference product Baraclude 1 mg film-coated tablets (Bristol Myers Squibb Pharma EEIG, United Kingdom).

The choice of the reference product
The choice of the European 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 Vocate 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 Vocate 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 randomised, open label, two treatment, single period, parallel design, bioequivalence study was carried out under fasted conditions in 60 healthy subjects, aged 19-43 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. An equal amount of subjects (n=30) received the test formulation compared to the reference formulation.

Blood samples were collected at pre-dose and at: 0.17, 0.33, 0.50, 0.67, 0.83, 1.00, 1.25, 1.50, 1.75, 2.0, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

The design of the study is acceptable. A crossover design with a sufficiently long washout may also be suited to show bioequivalence for entecavir. The plasma concentration decreases in a bi-exponential manner, resulting is a rapid decrease of plasma concentrations. Therefore the carry over effect is minimised rapidly. However, a long termination half life can be a valid reason for choosing a parallel

design providing that both the design and the statistical analyses are scientifically sound. Since this was the case, the design was found the be acceptable.

Entecavir may be taken without reference to food intake. From the literature it is known that food does not interact with the absorption of entecavir. 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
All 60 subjects were eligible for pharmacokinetic analysis. The MAH compared the relevant demographic data from the two groups. Analyses indicate that there were no significant differences between the two groups.

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

Treatment N=60	**AUC_{0-t}** ng.h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	26.74 ± 4.13	9.63 ± 2.58	0.67 (0.50 – 1.50)
Reference	27.30 ± 3.99	9.90 ± 1.64	0.67 (0.50 – 2.00)
***Ratio (90% CI)**	0.98 (0.92 – 1.04)	0.95 (0.87 – 1.05)	--
CV (%)	14.40	22.21	--

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
$t_{1/2}$	half-life
CV	coefficient of variation

**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 Vocate 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 Vocate.

- Summary table of safety concerns as approved in RMP

Important identified risks	- Exacerbation of hepatitis - ETV resistance - Emergence of resistant HUV/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 - 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 (content) and Levetiracetam Hetero 750 mg film-coated tablets (design and lay-out). 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 Vocate 0.5 mg and 1 mg, film-coated tablets have a proven chemical-pharmaceutical quality and are generic forms 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 Vocate with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 14 February 2018.

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