

Public Assessment Report

Scientific discussion

**Entecavir Sandoz 0.5 mg and 1 mg, film-coated
tablets**

(entecavir monohydrate)

NL/H/3848/001-002/DC

Date: 2 October 2017

This module reflects the scientific discussion for the approval of Entecavir Sandoz 0.5 mg and 1 mg, film-coated tablets. The procedure was finalised on 12 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

ALT	Alanine Aminotransferase
ASMF	Active Substance Master File
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
HBV	Hepatitis B Virus
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 Sandoz 0.5 mg and 1 mg, film-coated tablets from Sandoz B.V.

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 Belgium, Czech Republic, Greece, France, Ireland, Lithuania, Latvia 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 Sandoz is a film-coated tablet:

The 0.5 mg strength is a white, round, film-coated tablet debossed with “SZ” on one side and “108” on the other side.

The 1 mg strength is a pink, round, film-coated tablet with debossed with “SZ” on one side and “109” 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 OPA/Aluminium/PVC-Aluminium blisters and white HDPE bottles with polypropylene child resistant screw cap.

The excipients are:

Tablet core - lactose monohydrate, microcrystalline cellulose, crospovidone (Type A) and magnesium stearate.

Tablet coating - hypromellose 2910, macrogol 6000, titanium dioxide (E171) and talc. The 1 mg strength additionally contains iron oxide red (E172) and iron oxide yellow (E172).

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 white to off white powder. It is considered a high solubility drug (BCS Class III). Entecavir monohydrate possesses three chiral centres. The Ph.Eur. monograph does report the existence of polymorphism (anhydrous and monohydrate). For the current application it is isolated in the monohydrate form.

Two Active Substance Master File (ASMF) procedures are 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 manufacturers 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 is described in the ASMFs. For manufacturer-I the manufacturing process consists of seven steps followed by recrystallization. For manufacturer-II the manufacturing process consists of four steps. The starting materials of both manufacturers 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 drug substance specification complies with the Ph.Eur. with exception of the limits for a specified impurity. This is acceptable. Additional tests concern enantiomeric and isomeric purity, residual solvents and particle size and microbiological control which are in accordance with the ASMFs. Batch analyses data of one production batch of manufacturer-I and two production batches of manufacturer-II have been provided demonstrating compliance with the specification. In addition two production scaled batches of manufacturer-I and three production scaled batches of manufacturer-II have been provided demonstrating compliance with a former specification prior to the Ph.Eur. monograph. The additional batches tested according to the specification prior to the Ph.Eur. monograph are considered to be supportive to the batches tested with the proposed specifications.

Stability of drug substance

For manufacturer-I stability data of three batches have been provided in accordance with applicable European guidelines. The batches were stored at accelerated conditions (40°C/75% RH) for 6 months. The same batches as included in the accelerated studies were also included in the long term studies (25°C/60% RH) for 36 months. No trends have been observed. Based on the provided stability data the proposed retest period of 36 months when stored under the stated conditions is accepted.

For manufacturer-II stability data of seven production scaled batches have been provided in accordance with applicable European guidelines. The batches tested are non-micronized batches and micronized batches. The micronized batches originate from the non-micronized batch mentioned. The batches were stored at accelerated conditions (40°C/75% RH) up to 12 months. The same batches as included in the accelerated studies were also included in the long term studies. The non-micronized batches were stored up to 48 months and the micronized batches up to 36 months at 25°C/60% RH. Based on the data submitted, a retest period could be granted of 48 months for non-micronized and 36 months for micronized 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 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. 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 biowaiver of strengths has been justified based on the results of *in vitro* dissolution studies (>85% in 15 minutes at three different pH levels).

Manufacturing process

The manufacturing process consists of premixture preparations, powder mixture preparation, blending, compression, coating and packaging. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three production scaled batches of both strengths in accordance with the relevant European guidelines.

Control of excipients

All excipients comply with their respective Ph.Eur. monograph or a national Pharmacopoeia. 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, dimensions, identification, uniformity of dosage units, dissolution, related substances, assay and microbial quality. The test for microbial quality is performed non routinely. 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 nine 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 22 full scale batches (14 batches of the 0.5 mg strength and eight of the 1 mg strength). The drug product was stored at 25°C/60% RH (up to 36 months), 30°C/65% RH (up to 36 months) and 40°C/75% RH (six months). No trends or out of specification results were observed at accelerated, intermediate and long term conditions. A shelf life of 24 months without any storage precaution is considered as justified for the 0.5 mg and 1 mg entecavir film-coated tablets packed in the HDPE bottles and a shelf life of 36 months without any storage precaution is justified for the Alu/Alu blisters. The drug product was shown to be photostable, as no significant changes were observed in the tested parameters when directly exposed to UV and fluorescent light.

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 Sandoz 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 Sandoz 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 Sandoz 1 mg, film-coated tablets (Sandoz 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 Sandoz 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 Sandoz 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 27-70 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 42 days.

Blood samples were collected pre-dose and at and at 0.167, 0.333, 0.500, 0.583, 0.667, 0.750, 0.833, 1.00, 1.25, 1.50, 2.00, 2.50, 3.00, 4.00, 6.00, 12.0, 24.0, 48.0 and 72.0 hours after administration of the products.

The design of the study is acceptable and in accordance with the guideline on the investigation of bioequivalence and the product-specific guidance. The washout period is sufficient. The sample scheme covered a period of 72 hours is sufficient to estimate pharmacokinetic parameters of interest (C_{max} and AUC_{0-t}). Also, 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 did not complete the study. Therefore 25 subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean $\pm$ 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	31382 $\pm$ 6226	11387 $\pm$ 2291	0.67 (0.33 -2.50)
Reference	31886 $\pm$ 6156.3	11671 $\pm$ 2663	0.75 (0.33-3.00)
*Ratio (90% CI)	0.98 (0.96 – 1.01)	0.98 (0.92 – 1.05)	--
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} and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Entecavir Sandoz 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 Sandoz.

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 • Use in elderly patients (≥65 years of age) • Use in severe acute exacerbation of chronic hepatitis B
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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 PL of 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 Sandoz 0.5 mg and 1 mg, film-coated tablets have 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 Sandoz with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 12 April 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