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Public Assessment Report

Scientific discussion

Entecavir Zentiva lab 0.5 mg
Entecavir Zentiva lab 1 mg

ENTECAVIR MONOHYDRATE

CZ/H/708/01-02/DC

Date: 30.8.2017

This module reflects the scientific discussion for the approval of Entecavir Zentiva lab 0.5 mg and 1 mg. The procedure was finalised at 11.5.2017. For information on changes after this date please refer to the module 'Update'.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Entecavir Zentiva lab 0.5 mg and 1 mg, film-coated tablets, from Zentiva k.s., the Czech Republic

The product is indicated for:
Adults:
Treatment of chronic hepatitis B virus (HBV) infection (see section 5.1) 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 (see section 4.4).

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. With respect to patients with lamivudine-refractory hepatitis B, see sections 4.2, 4.4 and 5.1.

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. With respect to the decision to initiate treatment in paediatric patients, see sections 4.2, 4.4, and 5.1.

A comprehensive description of the indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC. The concerned member state involved in this procedure was UK.

The original and reference medicinal product is Baraclude 1 mg (0.5 mg) film-coated tablets from Bristol-Myers Squibb Pharma, authorised since 2006-06-26 through centralised procedure (EU/1/06/343).

The medicinal product contains Entecavir monohydrate as the active substance. Entecavir is an antiviral drug belonging to the group of Nucleoside analogue Reverse-Transcriptase Inhibitors (NRTI) with a very limited spectrum of antiviral activity. It selectively inhibits three specific functions of HBV DNA polymerase (priming of the HBV DNA polymerase, reverse transcription of the negative strand from the pre-genomic RNA, and synthesis of the positive strand). Entecavir acts as a faulty substrate and is incorporated into the viral DNA chain. Incorporation of entecavir induces a structure changes leading to the cessation of the synthesis of the DNA chain. Antiviral effect of entecavir is demonstrated as a decrease in serum HBV DNA levels.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

No Paediatric Investigation Plan (PIP) has been submitted.

II. QUALITY ASPECTS

II.1 Introduction

Two strengths of the finished product were authorised: 0.5 mg & 1 mg film-coated tablets.
Excipients are lactose monohydrate, microcrystalline cellulose, crospovidone, magnesium stearate in the core and film coating Opadry white including titanium dioxide, hypromellose, macrogol and polysorbate 80.
The product does not contain either TSE-risk or GMP components except for lactose and magnesium stearate. However, Public Statement evaluates BSE risk in pharmaceutical grade lactose as negligible (EMEA/CPMP/571/02) and the magnesium stearate is of vegetable origin.

Entecavir Zentiva lab 0.5 mg film-coated tablets are white to off white, round, biconvex film-coated tablets with diameter approx. 6.6 mm, plain on both side.
Entecavir Zentiva lab 1 mg film-coated tablets are white to off white, round, biconvex film-coated tablets with diameter approx. 8.4 mm with score line on one side, plain on the other side.
The score line used for strength 1 mg Entecavir Zentiva lab was discussed and justified. This score line is just to differentiate the strength and for aesthetic purpose only.
Both strengths are packed into OPA/Alu/PVC-Alu blisters as primary packaging and paper folding box.

II.2 Drug Substance

Entecavir monohydrate is manufactured by one source; ASMF procedure is used and respective letter of access was submitted.

Entecavir monohydrate is described in the Ph. Eur. (monograph 2815). The active substance is practically insoluble in water, anhydrous ethanol and heptane and slightly soluble in methanol. Entecavir shows polymorphism and its structure was confirmed by means of different analytical techniques. Impurities were characterized and genotoxicity study submitted with reference to ICH M7.

Synthesis of the active substance has been described in a seven-step synthesis followed by twice recrystallization. Starting materials were accepted.

The control tests and specifications for drug substance product are adequately drawn up. Quality of the final active substance conforms to the regulatory specification provided within the ASMF. This fact is supported by the results of several production batches.

Principally, methods have been described sufficiently and validated per ICH guidelines Q2A and Q2B if applicable. Related substances and assay are routinely tested via validated and stability indicating HPLC method. Two validated in-house GC methods for residual solvents have been developed.

Container closure system of Entecavir monohydrate includes double-layer medicinal polyethylene plastic bags (from LDPE) and aluminium tin. Polyethylene bags are the primary packaging for Entecavir monohydrate.

There were provided long-term and accelerated stability studies according ICH requirements. No significant changes in any parameters were observed. Potential impurities in stress study has been adequately discussed by supplier of active substance. The proposed retest period of 3 years is acceptable.

As for control of Entecavir monohydrate by the finished product manufacturer, the specification is satisfactory.

The risk benefit assessment is considered positive regarding the drug substance.

II.3 Medicinal Product

The development and manufacture of the product has been described, the choice of excipients is justified and their functions explained. Particle size distribution has been discussed. The dissolution method proposed for quality control of the finished product is acceptable. The discriminating power of dissolution method was demonstrated. Biowaiver for 0.5 mg strengths has been applied and based on the composition, manufacture and properties of the finished product it has been accepted.

Manufacture of the finished product has been described including final film coating and packaging, batch size was stated and a control of critical steps was submitted in the dossier. Several pilot and scale-up batches were used for process validation. Based on the results, it was concluded that the manufacturing process is verified and can be used for further commercial batches. Information about control of all excipients is satisfactory.

The product specifications cover appropriate parameters for this dosage form (description, identification, uniformity of dosage units, disintegration, dissolution, assay, related substances, microbial contamination). Validations of the analytical methods have been presented. Batch analysis has been performed for three batches of every strength. The batch analysis results show that the finished product meets the proposed specifications.

Characterization of impurities has been provided and it was shown that impurities are carefully monitored. Reference standards were detailed, summary of reference standards and working materials have been given.

Specifications for the packaging components, including IR methods for identification of the plastic components are enclosed. The components are safe for contact with food and pharmaceuticals.

The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for drug product are adequately drawn up. Blisters proposed for routine storage are the same as those which have been used in the stability studies supporting the shelf-life. The stability studies demonstrate suitability of the chosen packaging materials. The proposed shelf-life of 24 months with no special storage conditions for drug product is considered acceptable. Photo-stability data and stress study data to support the proposed shelf-life have been presented.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture, control of the active substance and finished product has been satisfactorily presented. The results of tests indicate satisfactory consistency and uniformity of drug product characteristics and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinical setting.

III. NON-CLINICAL ASPECTS

III.1 Introduction

Pharmacodynamic, pharmacokinetic and toxicological properties of entecavir are well known. As entecavir is a widely used, well-known active substance, the applicant has not provided additional studies and further studies are not required. The overview based on literature review is, thus, appropriate.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Entecavir Zentiva lab 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.

IV. CLINICAL ASPECTS

IV.1 Introduction

To support the application, the applicant has submitted one bioequivalence study. Entecavir Zentiva lab as well as Baraclude are immediately released formulations, thus, one bioequivalence study is adequate according to the BE guideline (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**.).

IV.2 Pharmacokinetics

The results of bioequivalence study ETI-P1-466 (15/11/ENT/BSD) are presented as follows:

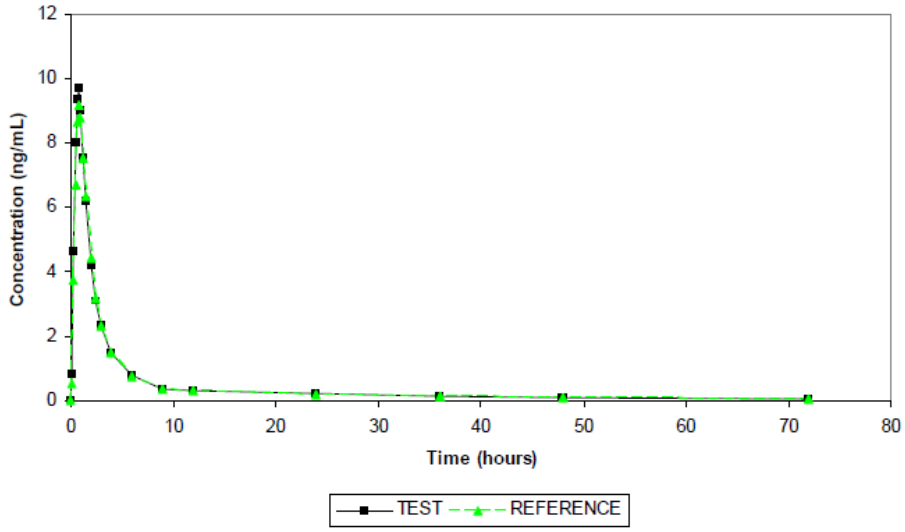
Table 1: Pharmacokinetic parameters for Entecavir (non-transformed values; arithmetic mean ± SD, t_{max} median, range)

Treatment	AUC_{0-72} g/ml/h	$AUC_{0-\infty}$ xg/ml/h	C_{max} g/ml	t_{max} h
Test (N=30)	29.34 ± 7.72	33.68 ± 8.16 *(considered N=28)*	10.65 ± 2.47	0.67 (0.50 – 1.50)
Reference (N=30)	28.90 ± 7.50	33.29 ± 8.25 *(considered N=28)*	10.26 ± 2.45	0.83 (0.50 – 1.50)
*Ratio (90% CI)	101.78% (98.79%, 104.87%)	101.62% (98.28%, 105.07%)	104.96% (99.00%, 111.27%)	

AUC_{0-72h}	Area under the plasma concentration curve from administration to last observed concentration at time 72 hours.
$AUC_{0-\infty}$	Area under the plasma concentration curve extrapolated to infinite time.
C_{max}	Maximum plasma concentration
t_{max}	Time until Cmax is reached

**ln-transformed values*

Figure 1: Linear profile of the mean - Entecavir



The occurrence of AEs was similar in both groups. No severe AE or serious AE were observed during the study. It can be concluded that the two formulations are well tolerated.

Conclusion on bioequivalence study:

Based on the submitted bioequivalence study, the Test formulation (Entecavir Zentiva lab 1 mg Film-Coated Tablets, Zentiva, k.s., Czech Republic) is considered to be bioequivalent to the Reference formulation (Baraclude 1 mg Film-Coated Tablets, Bristol-Myers Squibb Pharmaceuticals, Ltd. DE).

Biowaiver:
The results of study ETI-P1-466 with 1 mg formulation could be extrapolated to the strength of 0.5 mg, as all requirements stated in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6 were met.

IV.3 Pharmacodynamics

N/A

IV.4 Clinical efficacy

N/A

IV.5 Clinical safety

N/A

IV.6 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 Zentiva lab 0.5 mg and Entecavir Zentiva lab 1 mg.

- Summary table of safety concerns as approved in RMP version 1.3

Important identified risks	On treatment and post-treatment exacerbation of hepatitis 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	Safety in pregnancy and breastfeeding Safety in paediatric population Safety in elderly patients (≥65 years of age) Safety in patients with severe acute exacerbation of CHB Long-term safety and clinical outcomes data

Routine pharmacovigilance was suggested and no additional pharmacovigilance activities were proposed by the Applicant, this is endorsed.

Routine risk minimisation measures are considered satisfactory to minimise the risks of this medicinal product.

IV.7 Discussion on the clinical aspects

To support the application, the applicant has submitted one bioequivalence study. No further specific clinical studies have been performed, as the application is submitted in accordance with Article 10.1 of Directive 2001/83/EEC as amended. Entecavir is a widely used, well-known active substance, therefore, the submitted Clinical overview based on literature review is adequate.

Based on the submitted data, Entecavir Zentiva lab 1 mg Film-Coated Tablets is considered bioequivalent with Baraclude 1 mg Film-Coated Tablets and the results can be extrapolated to the other strength (0.5 mg).

V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report. The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the risk-benefit ratio for the applications for Entecavir Zentiva lab 0.5 mg and 1 mg, film-coated tablet was considered positive.

The SmPC, PIL and labelling are satisfactory.

To support the application, the applicant has submitted one bioequivalence study.

Agreement between Member States was reached during the procedure. There was no discussion at CMDh. The decentralised procedure was finalised with a positive outcome on 11.5.2017.

No conditions pursuant to Article 21a or 22 of Directive 2001/83/EC have been made during the procedure.