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Public Assessment Report

Scientific discussion

Entecavir Pharmascience International Ltd.
Entecavir

DK/H/2617/001-002/DC

Date: 06-02-2018

This module reflects the scientific discussion for the approval of Entecavir Pharmascience International Ltd. The procedure was finalised on 08-06-2017. 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, Entacavir Pharmascience International Ltd., 0.5 mg and 1 mg film-coated tablets from Pharmascience International Ltd.

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 Spain and Romania.

The applicant has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Baraclude 1 mg film-coated tablets by Bristol-Myers Squibb Pharma EEIG, registered in Germany. This generic product can be used instead of its reference product.

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

II. QUALITY ASPECTS

II.1 Introduction

Entecavir Pharmascience International Ltd. 0.5 mg is a white to off-white triangular shaped tablet.

Entecavir Pharmascience International Ltd. 1 mg is a pink triangular shaped tablet.

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

The film-coated tablets are packed in aluminium blisters (pack sizes of 30) and white HDPE bottle with child resistant polypropylene screw cap and dessicant packet (30 tablets).

Description of excipients as described in the SmPC/PL.

Compliance wih Good Manufacturing Practice

The RMS has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacture and assembly of this product prior to granting its national authorisation.

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.

The chemical-pharmaceutical documentation and Quality Overall Summary in relation to Entecavir Pharmascience are in general of sufficient quality in view of the present European regulatory requirements.

The drug substance complies with its respective Ph.Eur monograph. The overall control strategy, analytical methodology and stability are considered suitable.

The Active Substance Master File (ASMF) procedure is used for the active substance.
Based on the presented stability studies, an appropriate re-test period has been set.

II.3 Medicinal Product

The development of the product has been described, the choice of excipients is justified and their functions explained.

The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented.

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.

Photostability is demonstrated for the product in marketed packaging.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Entecavir Pharmascience International Ltd. has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

III. NON-CLINICAL ASPECTS

III.1 Introduction

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

The non-clinical overview report refers 17 publications up to year 2014. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Since Entacevir 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.3 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-todate 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. As entecavir is a widely used, well-known active substance, the applicant has not provided additional studies (apart from a supportive bioequivalence study referenced below) and further studies are not required. Overview based on literature review is, thus, appropriate.

The clinical report refers 19 publications up to 2014. The clinical overview on the clinical pharmacology, efficacy and safety is adequate.

IV.2 Pharmacokinetics

For this generic application, the MAH has submitted 1 bioequivalence study in which the pharmacokinetic profile of the test product Entecavir is compared with the pharmacokinetic profile of the reference product Baraclude 1 mg, film-coated tablets (Bristol-Myers Squibb Pharma EEIG, Germany).

The application concerns the strengths 0.5 mg and 1 mg, which are quantitatively proportional in composition. The criteria for waiver of bioequivalence studies with the 0.5 mg strength are considered fulfilled.

Bioequivalence studies

The study was an open-label, randomized, two-treatment, two-sequence, two-period, two-way crossover, single-dose bioavailability study conducted under fasting conditions with a wash out period of 30 days between the two administrations. One tablet of 1 mg was administered in each period.

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

PARAMETER	TEST		REFERENCE		F-value (treatment)	p -value$
	MEAN	C.V. (%)	MEAN	C.V.(%)		
AUC_{0-72} (ng.h/mL)	31.4455	20.7	31.9296	20.6	N.A.	N.A.
$ln(AUC_{0-72})$	3.4290	5.8	3.4438	5.8	2.08	N.S.
$AUC_{0-\infty}$ (ng.h/mL)	37.2752	19.5	37.9366	20.7	N.A.	N.A.
$ln(AUC_{0-\infty})$	3.6013	5.1	3.6164	5.5	2.00	N.S.
C_{max} (ng/mL)	10.5452	34.9	10.3070	36.4	N.A.	N.A.
$ln(C_{max})$	2.2983	15.0	2.2688	16.2	0.25	N.S.
T_{max} (h)*	0.67	46.2	0.75	42.5	N.A.	N.A.
λ_z (1/h)	0.0174	12.5	0.0174	12.8	N.A.	N.A.
$t_{½}$ (h)	40.52	14.0	40.42	12.7	N.A.	N.A.
AUC_{0-72} /$AUC_{0-\infty}$ (%)	84.2	3.8	84.2	3.9	N.A.	N.A.

*The median is presented; N.A. = Not Applicable and N.S. = Not Significant;

$ = significant whenever p-value <0.05.

Conclusion on bioequivalence studies:
All outstanding issues have been adequately resolved.
Based on the submitted bioequivalence study Entecavir Pharmascience International 1 mg tablets is considered bioequivalent with Baraclude 1 mg tablets by Bristol Meyer-Squibb.

The results of study 547-12 with 1 mg formulation can be extrapolated to other strengths, 0.5 mg, according to conditions in Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev. 1/Corr*, section 4.1.6

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 Pharmascience International Ltd..

Table 1: Summary of safety concerns as approved in the DCP

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
Important 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

Table 2: Summary of risk minimisation measures as approved in the DCP

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Exacerbation of hepatitis	Labeling: • Spontaneous exacerbations in chronic hepatitis B are relatively common and are characterised by transient increases in serum ALT. • After initiating antiviral therapy, serum ALT may increase in some patients as serum HBV DNA levels decline liver disease or cirrhosis may be at a higher risk for hepatic decompensation following hepatitis exacerbation, and therefore should be monitored closely during therapy. • Acute exacerbation of hepatitis has also been reported in patients who have discontinued hepatitis B therapy. Posttreatment exacerbations are usually associated with rising HBV DNA, and the majority appears to be self-limited. However, severe exacerbations, including fatalities, have been reported. • Listed in section 4.4 and 4.8 Prescription only medicine	None proposed
Entecavir resistance	Labeling: • Mutations in the HBV polymerase that encode lamivudine-resistance substitutions may lead to the subsequent emergence of secondary substitutions, including those associated with entecavir associated resistance (ETVr). In a small percentage of lamivudine-refractory patients, ETVr substitutions at residues rtT184, rtS202 or rtM250 were present at baseline. Patients with lamivudine-resistant HBV are at higher risk of developing subsequent entecavir resistance than patients without lamivudine resistance. • When starting therapy in patients with a documented history of lamivudine-resistant HBV, combination use of entecavir plus a second antiviral agent (which does not share cross-resistance with either lamivudine or entecavir) should be considered in preference to entecavir monotherapy. • In patients with decompensated liver disease, virologic breakthrough may be associated with serious clinical complications of the underlying liver disease. Therefore, in patients with both decompensated liver disease and lamivudine-resistant HBV, combination use of entecavir plus a second antiviral agent (which does not share cross-resistance with either lamivudine or entecavir)	None proposed

	should be considered in preference to entecavir monotherapy. • Listed in section 4.4 Prescription only medicine	
Emergence of resistant HIV in HIV/HBV co-infected patients not concurrently receiving effective HIV treatment	Labeling: • Patients with decompensated liver disease: a higher rate of serious hepatic adverse events has been observed in patients with decompensated liver disease, in particular in those with Child-Turcotte-Pugh (CTP) class C disease, compared with rates in patients with compensated liver function. Also, patients with decompensated liver disease may be at higher risk for lactic acidosis and for specific renal adverse events such as hepatorenal syndrome. Therefore, clinical and laboratory parameters should be closely monitored in this patient population • Entecavir has been studied in 68 adults receiving a lamivudine-containing HAART regimen. • No data are available on the efficacy of entecavir in HBeAg negative patients coinfected with HIV. There are limited data on patients co-infected with HIV who have low CD4 cell counts (< 200 cells/mm3). • Listed in section 4.4 and 5.1. Prescription only medicine	None proposed
Carcinogenicity	Labeling: • Two-year carcinogenicity studies: in male mice, increases in the incidences of lung tumours were observed at exposures ≥ 4 and ≥ 2 times that in humans at 0.5 mg and 1 mg respectively. Tumour development was preceded by pneumocyte proliferation in the lung which was not observed in rats, dogs, or monkeys, indicating that a key event in lung tumour development observed in mice likely was species specific. Increased incidences of other tumours including brain gliomas in male and female rats, liver carcinomas in male mice, benign vascular tumours in female mice, and liver adenomas and carcinomas in female rats were seen only at high lifetime exposures. However, the no effect levels could not be precisely established. The predictivity of the findings for humans is not known. • Listed in section 5.3 Prescription only medicine	None proposed
Mitochondrial toxicity	Labeling: • Entecavir carries a warning for the risk of lactic acidosis and severe hepatomegaly with steatosis. [5.4 Lit. Ref. Baraclude® SPC, 2014] This effect, considered a class effect for oral nucleos(t)ide analogues, is based on the potential for mitochondrial toxicity due to the incorporation of the nucleoside analogs into the mitochondrial DNA by DNA polymerase-gamma.	None proposed

	• Mitochondrial DNA damage is permanent and leads to an impaired oxidative phosphorylation and cell death. In vitro studies of various entecavir concentrations did not influence mitochondrial DNA expression, likely due to poor entecavir binding to mitochondrial DNA and, therefore, lack of inhibitory effects on mitochondrial respiratory function. No mitochondrial toxicities were noted in clinical trials of Entecavir to date. • Listed in the clinical overview of Entecavir section 2.5.5.4 Prescription only medicine	
Long term safety and clinical outcomes data	Labeling: • In HBeAg negative adult patients, treatment should be administered at least until HBs seroconversion or there is evidence of loss of efficacy. With prolonged treatment for more than 2 years, regular reassessment is recommended to confirm that continuing the selected therapy remains appropriate for the patient. • The benefits of long-term virologic suppression with continued therapy must be weighed against the risk of prolonged treatment, including the emergence of resistant hepatitis B virus. Liver biopsy results: 57 patients from the pivotal nucleoside-naive studies 022 (HBeAg positive) and 027 (HBeAg negative) who enrolled in a long-term rollover study were evaluated for long-term liver histology outcomes. The entecavir dosage was 0.5 mg daily in the pivotal studies (mean exposure 85 weeks) and 1 mg daily in the rollover study (mean exposure 177 weeks), and 51 patients in the rollover study initially also received lamivudine (median duration 29 weeks). Of these patients, 55/57 (96%) had histological improvement as previously defined (see above), and 50/57 (88%) had a ≥ 1-point decrease in Ishak fibrosis score. For patients with baseline Ishak fibrosis score ≥ 2, 25/43 (58%) had a ≥ 2-point decrease. All (10/10) patients with advanced fibrosis or cirrhosis at baseline (Ishak fibrosis score of 4, 5 or 6) had a ≥ 1 point decrease (median decrease from baseline was 1.5 points). At the time of the long-term biopsy, all patients had HBV DNA < 300 copies/ml and 49/57 (86%) had serum ALT ≤ 1 times ULN. All 57 patients remained positive for HBsAg. • Listed in section 4.2 and 5.1 Prescription only medicine	None proposed
Use in the paediatric population	Labeling: • The decision to treat paediatric patients should be based on careful consideration of individual patient needs and with reference to current paediatric treatment guidelines including the value of baseline histological information. The benefits of long-term virologic suppression with continued	None proposed

	therapy must be weighed against the risk of prolonged treatment, including the emergence of resistant hepatitis B virus. • Serum ALT should be persistently elevated for at least 6 months prior to treatment of paediatric patients with compensated liver disease due to HBeAg positive chronic hepatitis B; and for at least 12 months in patients with HBeAg negative disease. • Listed in section 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 Prescription only medicine	
Use in pregnancy	Labeling: • There are no adequate data from the use of entecavir in pregnant women. • Studies in animals have shown reproductive toxicity at high doses • The potential risk for humans is unknown. Entecavir Pharmascience International LTD should not be used during pregnancy unless clearly necessary. • There are no data on the effect of entecavir on transmission of HBV from mother to newborn infant. Therefore, appropriate interventions should be used to prevent neonatal acquisition of HBV. • Listed in section 4.6 and 5.3. Prescription only medicine	None proposed
Use in elderly patients (≥65 years of age)	Labeling: • The effect of age on the pharmacokinetics of entecavir was evaluated comparing elderly subjects in the age range 65-83 years (mean age females 69 years, males 74 years) with young subjects in the age range 20-40 years (mean age females 29 years, males 25 years). AUC was 29% higher in elderly than in young subjects, mainly due to differences in renal function and weight. After adjusting for differences in creatinine clearance and body weight, elderly subjects had a 12.5% higher AUC than young subjects. The population pharmacokinetic analysis covering patients in the age range 16- 75 years did not identify age as significantly influencing entecavir pharmacokinetics. • Listed in section 5.2. Prescription only medicine	None proposed
Use in severe acute exacerbation of chronic hepatitis B	Labeling: • Spontaneous exacerbations in chronic hepatitis B are relatively common and are characterised by transient increases in serum ALT. • To differentiate between elevations in aminotransferases due to response to treatment and increases potentially related to lactic acidosis, physicians should ensure that changes in ALT are associated with improvements in other laboratory markers of chronic hepatitis B. • Listed in section 4.4 and 4.8	None proposed

	Prescription only medicine	

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 language used for the purpose of user testing the PIL was English.
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.

The test consisted of: a pilot test with 2 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Entecavir Pharmascience International Ltd. 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 MAH presented a risk management plan summarising the safety concerns. There are no additional pharmacovigilance or risk minimisation measures.

Agreement between Member States was reached during a written procedure. There was no discussion in the CMD(h). The Concerned Member States, on the basis of the data submitted, considered that essential similarity has been demonstrated for Entecavir Pharmascience International Ltd. with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised on 08.06.2017.
Entecavir Pharmascience International Ltd. was authorised in RMS 06-07-2017

According to the List of Union reference dates and frequency of submission of periodic safety update reports (PSURs), no routine PSURs are required for this product.

There were no post-approval commitments made during the procedure.