Public Assessment Report

Scientific discussion

Entecavir Aristo

DK/H/2740/01-02/DC

Date: 15-03-2018

This module reflects the scientific discussion for the approval of Entecavir Aristo. The procedure was finalised on 06-07-2017. 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 Aristo, 0.5 mg and 1 mg film-coated tablets from Aristo Pharma GmbH.

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 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 Germany, Italy, Spain and UK.

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 Aristo 0.5 mg is a white to off white triangular shaped tablet.

Entecavir Aristo 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 90 tablets) and white HDPE bottle with PP child resistant cap and induction sealing (30 tablets).

Description of excipients as described in the SmPC/PL.

Compliance with 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 a white or almost 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 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 process validation has been submitted.

The product specifications cover appropriate parameters for this dosage and all acceptance criteria are found justified. 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. Sufficient amount of batches have been submitted for each strength, shelf life of 2 years is accepted, no special storage condition.

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 Aristo has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

One post-approval commitment was made:
The applicant commits to perform stability data for product near the end of the shelf life. As previous in-use stability did not reveal any instability issues, and the available stability data for the drug product suggests the same (stable product). It is accepted that the applicant should submit the data only if any changes to the in-use stability are needed, otherwise 30 days are accepted.

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. Overview based on literature review is, thus, appropriate.

The non-clinical overview report refers 31 publications up to year 2015. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Since Entecavir 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-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. 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 20 publications up to 2016. 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 60 days between the two administrations. One film-coated tablet of 1 mg was administered in each period.

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

Parameters (Units)	Arithmetic Mean ± SD (%CV) (N = 40)	
	Reference product (R)	Test product (T)
C_{max} (ng/mL)	10.171 ± 2.4788 (24.37%)	10.479 ± 2.1925 (20.92%)
$^{\#}T_{max}$ (hr)	0.830 (0.50 - 2.25)	0.830 (0.50 - 2.25)
AUC_{0-72} (hr*ng/mL)	31.193 ± 5.8690 (18.82%)	30.297 ± 5.5284 (18.25%)
$t_{½}$ (hr)	44.625 ± 20.7508 (46.50%)	42.762 ± 21.1543 (49.47%)
λ_z (1/hr)	0.0225 ± 0.02959 (131.67%)	0.0226 ± 0.02759 (121.82%)

$^{\#}$ For T_{max} median (min – max)

Conclusion on bioequivalence studies:
Based on the submitted bioequivalence study Entecavir Aristo 1 mg tablets from Aristo Pharma GmbH is considered bioequivalent with Baraclude 1 mg tablets by Bristol Meyer-Squibb.

The results of study 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 Aristo
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Table 1: Summary of safety concerns as approved in the DCP

Summary of safety concerns	
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 old) • Use in severe acute exacerbation of chronic hepatitis B (CHB)

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	SmPC sections 4.4 and 4.8 PIL sections 2 and 3 Prescription only medicine	None proposed
Entecavir resistance	SmPC sections 4.4 and 5.1	None proposed

	PIL sections 2 and 3 Prescription only medicine	
Emergence of resistant HIV in HIV/HBV co-infected patients not concurrently receiving effective HIV treatment	SmPC sections 4.4 and 5.1 Prescription only medicine	None proposed
Carcinogenicity	SmPC section 5.3 Prescription only medicine	None proposed
Mitochondrial toxicity	SmPC section 5.1 Prescription only medicine	None proposed
Long term safety and clinical outcomes data	Routine pharmacovigilance Prescription only medicine	None proposed
Use in the paediatric population	SmPC sections 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 PIL sections 2 and 3 Prescription only medicine	None proposed
Use in pregnancy	SmPC section 4.6 PIL section 2 Prescription only medicine	None proposed
Use in elderly patients (≥ 65 years old)	SmPC sections 4.2 and 5.2 Prescription only medicine	None proposed
Use in severe acute exacerbation of chronic hepatitis B (CHB)	Routine pharmacovigilance Prescription only medicine	None proposed

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 4 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 Aristo 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 Aristo with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised on 06-07-2017. Entecavir Aristo was authorised in RMS on 01-09-2017.

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.

The following post-approval commitments have been made during the procedure:

The applicant commits to perform stability data for product near the end of the shelf life. As previous in-use stability did not reveal any instability issues, and the available stability data for the drug product suggests the same (stable product). It is accepted that the applicant should submit the data only if any changes to the in-use stability are needed, otherwise 30 days are accepted