

Public Assessment Report

Scientific discussion

**Entecavir Klinge 0.5 mg and 1 mg
film-coated tablets**

(entecavir monohydrate)

NL/H/3846/001-002/DC

Date: 5 September 2017

This module reflects the scientific discussion for the approval of Entecavir Klinge 0.5 mg and 1 mg film-coated tablets. The procedure was finalised on 20 March 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

ASMF	Active Substance Master File
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 Klinge 0.5 mg and 1 mg film-coated tablets from Klinge 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 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 Germany.

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

II. QUALITY ASPECTS

II.1 Introduction

Entecavir Klinge 0.5 mg is a white oval shaped tablet with a break line on both sides.

Entecavir Klinge 1 mg is a pink oval shaped tablet with a break line on both sides. The tablet can be divided into equal doses.

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.

The excipients are:

Tablet core – microcrystalline cellulose, lactose monohydrate, starch pregelatinised, crospovidone, magnesium stearate

Tablet coating – titanium dioxide (E171), hypromellose, macrogol 400, polysorbate 80; the 1 mg strength additionally contains red iron oxide E172

The two tablet cores 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 practically insoluble in water, anhydrous ethanol and heptane and slightly soluble in methanol.

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.

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 of entecavir monohydrate consists of seven steps followed by recrystallization. The proposed starting materials 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 MAH has adopted the specification of the ASMF-holder as drug substance specification, with an additional limit for particle size distribution. The specifications are considered acceptable. Batch analytical data demonstrating compliance with the drug substance specification has been provided for three batches of the active substance.

Stability of drug substance

No data has been provided by the MAH on the stability of the drug substance. The same re-test period and storage conditions are used as defined in the ASMF. The re-test period for the drug substance is 36 months.

II.3 Medicinal Product

Pharmaceutical development

The development of the drug product has been described, the choice of excipients is justified and their functions are explained. The same excipients as in the reference product were selected, except for povidone which was replaced with pregelatinised starch for stability reasons. 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. It has been demonstrated that the break line is functional and that the tablets can be divided into equal tablet halves. 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 pH and in the medium proposed for routine dissolution testing (phosphate buffer pH 6.8), support bioequivalence. For the 0.5 mg product strength, a bio-waiver of strengths has been justified based on the results of *in vitro* dissolution studies.

Manufacturing process

The manufacturing process includes premixture preparation, powder mixture preparation, (wet) granulation, blending, compression, coating and packaging steps. The process is considered a non-standard manufacturing process. Process validation of the drug product has been presented for three full scale commercial batches of both strengths.

Control of excipients

With the exception of the Opadry film coatings, all excipients comply with their respective Ph. Eur. monographs. For the Opadry film coatings, an in-house specification is included. These specifications are acceptable.

Quality control of drug product

The drug product specification includes tests for appearance, identification, uniformity of dosage units, disintegration, dissolution, water content, related substances, assay and microbial quality. The test for microbial quality is performed non-routinely. The release and shelf-life specifications are acceptable.

Batch analytical data from three commercial scale batches have been provided, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the drug product has been provided for three full scale batches of each tablet strength packed in Alu/Alu blister packs. The drug product was stored for up to eighteen months at $25 \pm 2^\circ\text{C}/60 \pm 5\% \text{ RH}$ and for up to eighteen months at $30 \pm 2^\circ\text{C}/65 \pm 5\% \text{ RH}$ and for six months at $40 \pm 2^\circ\text{C}/75 \pm 5\% \text{ RH}$. The submitted stability data show only little changes over time. The drug product was shown to be photostable, as no significant changes were observed in the tested parameters when the 0.5 mg tablets were directly exposed to UV and fluorescent light.

On the basis of the available stability data, the proposed shelf-life of 24 months with the storage condition 'Do not store above 30°C . Store in the original package.' can be granted.

Specific measures for the prevention of the transmission of animal spongiform encephalopathies

The only component of animal origin used in the drug product is lactose monohydrate. It has been confirmed that the lactose is produced from milk sourced from healthy cows in the same condition as milk collected for human consumption. The lactose has been prepared without the use of other ruminant material than calf rennet to the description as published in Public Statement EMEA/CPMP/571/02. The excipient lactose monohydrate is safe with the view of possible TSE/BSE risk.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Entecavir Klinge 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 Klinge 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 a 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 Klinge 1 mg (Klinge Pharma GmbH, Germany) is compared with the pharmacokinetic profile of the reference product Baraclude 1 mg, film-coated tablets (Bristol-Myers Squibb Pharma EEIG, UK).

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 Klinge 0.5 mg film-coated tablets based on the following arguments:

- The formulations are dose proportional.
- Both strengths of Entecavir Klinge are manufactured by the same manufacturer and the same process.
- Entecavir has linear pharmacokinetics over the therapeutic dose range.
- Dissolution for both strengths is very rapid ($\geq 95\%$ within 5 minutes) at three pHs (pH 1.0, 4.5 and 6.8).

Bioequivalence study

Design

A single-dose, randomised, two-period, two-treatment, two-sequence, crossover bioequivalence study was carried out under fasted conditions in 26 healthy male and female subjects, aged between 18 and 55 years. Each subject received a single dose (1 mg) of one of the 2 entecavir formulations. The tablet was orally administered with 240 ml water after an overnight fast of at least 10 hours. Fasting continued for at least 4 hours following drug administration. There were 2 dosing periods, separated by a washout period of 28 days.

Blood samples were collected pre-dose and at 0.17, 0.33, 0.5, 0.67, 0.83, 1, 1.25, 1.5, 1.75, 2, 3, 4, 6, 9, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

The study design is acceptable. The wash-out period of 28 days is long enough to prevent a carry over. Considering a terminal elimination half life of 128-149 hours, AUC truncated at 72 hours is considered acceptable parameter for determination of the absorption phase of an immediate release product. 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 discontinued the study due to emesis within the restriction period. The remaining 25 subjects completed the study and 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 ₀₋₇₂ pg.h/ml	C _{max} pg/ml	t _{max} h
Test	31939.6 \pm 43	10955.5 \pm 20	0.83 (0.50 – 1.50)
Reference	32198.6 \pm 43	10826.4 \pm 22	0.83 (0.50 – 1.50)

*Ratio (90% CI)	0.99 (0.97 – 1.01)	1.02 (0.95 – 1.09)	--
AUC₀₋₇₂ area under the plasma concentration-time curve from time zero to 72 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 AUC₀₋₇₂ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study Entecavir Klinge 1 mg is considered bioequivalent with Baraclude 1 mg film-coated tablets.

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 Klinge.

- Summary table of safety concerns as approved in RMP

Important identified risks	<ul style="list-style-type: none"> Exacerbation of hepatitis ETV resistance Emergence of resistant HIV in HIV/HBV co-infected patients not concurrently receiving effective HIV treatment
Important potential risks	<ul style="list-style-type: none"> Carcinogenicity Mitochondrial toxicity
Missing information	<ul style="list-style-type: none"> Long term safety and clinical outcomes data Use in the paediatric population Use in pregnancy and lactation 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

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 test consisted of a pilot test with 3 participants, followed by two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.

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.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Entecavir Klinge 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 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 Klinge with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 20 March 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