LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Entecavir Medical Valley
entecavir monohydrate, entecavir (anhydrous)

SE/H/2201/01-02

This module reflects the scientific discussion for the approval of Entecavir Medical Valley. The Public Assessment Report was written in August 2019 by the previous RMS (NL) after initial procedure NL/H/4408/001-002/DC and is attached at the end of this document. RMS transfer from NL to SE was completed 2021-12-07. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

Active substance	entecavir monohydrate
Pharmaceutical form	Film-coated tablets
Strength	0,5 mg; 1 mg
Applicant	Medical Valley Invest AB
EU-Procedure number (original)	NL/H/4408/001-002/DC

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval / non approval	Summary / Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Entecavir Xiromed 0.5 mg and 1 mg film-coated tablets

(entecavir monohydrate)

NL/H/4408/001-002/DC

Date: 22 August 2019

This module reflects the scientific discussion for the approval of Entecavir Xiromed 0.5 mg and 1 mg film-coated tablets. The procedure was finalised at 15 May 2019. 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
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
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
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 Xiromed 0.5 mg and 1 mg film-coated tablets from Medical Valley Invest AB.

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 (EU/1/06/343/001-007) which has been centrally registered in the EEA by Bristol-Myers Squibb Pharma EEIG since 26 June 2006 (original product).

The concerned member states (CMS) involved in this procedure were Germany, Denmark, Norway and Sweden.

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

II. QUALITY ASPECTS

II.1 Introduction

Entecavir Xiromed is a triangle shaped, biconvex film-coated tablet in two strengths:

- 0.5 mg film-coated tablets are white to off white, film- coated tablets debossed with ‘J' on one side and ‘110’ on other side.
- 1 mg film-coated tablets are pink, film-coated tablets debossed with 'J' on one side and '111' on other side.

The film-coated tablets contain as active substance 0.5 mg and 1 mg of entecavir, as monohydrate.

The film-coated tablets are packed in Alu/Alu blisters and high-density polyethylene (HDPE) bottle with child resistant polypropylene closure.

The excipients are:
Tablet core
- Calcium carbonate
- Pregelatinised starch
- Carmellose sodium
- Soy polysaccharides
- Citric acid monohydrate
- Sodium stearyl fumarate

Tablet coating
- Hypromellose
- Titanium dioxide (E171)
- Macrogol
- Polysorbate 80 (only 0.5 mg strength)
- Iron oxide red (E172) (only 1 mg strength)

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.). The active substance is insoluble in water. Entecavir monohydrate contains three stereogenic centres in its structure and is manufactured as a the pure 1S,3R,4S enantiomer. Entecavir shows polymorphism and is consistently manufactured having the same polymorphic form (monohydrate) that was demonstrated to remain stable during storage of the drug substance.

The Active Substance Master File (ASMF) procedure is initially 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.

During the procedure, the ASMF holder has replaced the ASMF by a valid CEP. The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process

The manufacturing process is described in six chemical transformation steps starting with two starting materials. No class 1 organic solvents are used in the manufacturing process. The active substance has been adequately characterised and acceptable specifications have been adopted for the starting materials, solvents and reagents.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. It includes additional requirements for identity, polymorphic identity and residual solvents that have been adopted from the active substance manufacturer as well as additional requirements for microbiological quality and particle size distribution by the finished product manufacturer. Batch analytical data demonstrating compliance with this specification have been provided for five batches.

Stability of drug substance

Stability data on the active substance have been provided for three full scaled batches stored at 25°C/60% RH (48 months) and 40°C/75% RH (six months) and a fourth full scaled batch that was only stored at 40°C/75% RH (six months). No clear trends or changes were seen at both storage conditions in the tested parameters. The drug substance was shown not to be light sensitive. Based on the data submitted, a retest period could be granted of 60 months without special storage 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 explained. The main development studies performed were the characterisation of the reference products, development of the dissolution method, formulation optimization studies and manufacturing process optimization studies. The choices of the packaging and manufacturing are considered justified. A bioequivalence study has been performed with the 1 mg product strength. For the 0.5 mg product strength a

biowaiver has been justified based on the results of *in vitro* dissolution studies. The test batch used in the bioequivalence study was manufactured according to the finalized composition and manufacturing process. The pharmaceutical development of the product has been adequately performed.

Manufacturing process

The main steps of the manufacturing process are the dry mixing of intragranular components, wet granulation using a solution of active substance in water, mixing with extra granular components and lubrication, compression, film-coating and packaging. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full scaled batches per strength in accordance with the relevant European guidelines.

Control of excipients

The excipients comply and are tested in accordance with their Ph.Eur. monographs, except for the non-compendial soy polysaccharides and the film-coating mixtures. Soy polysaccharides and the film-coating mixtures are controlled according to their manufacturer specifications. 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, identification, average mass, water content, dissolution, uniformity of dosage units, related substances, assay and microbiological examination. Except for water content and related substances, the release and shelf-life requirements are identical. 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 two full scale batches per strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product has been provided on three full scaled batches per strength that were stored at 25°C/60% RH (36 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in the proposed packaging. The stability data show an increase of impurities that was most pronounced at accelerated conditions. Dissolution seems to slightly decrease during storage of the drug product, mainly at accelerated conditions. No trends or changes were observed in any of the other tested parameters. On basis of the data submitted, a shelf life was granted of three years without any special storage conditions.

Stability data has been provided demonstrating that the product remains stable for 90 days following first opening of the 90's count HDPE container when stored at 25°C/60% RH and in-use conditions were simulated. The in-use stability study was repeated on batches after storage at long-term storage conditions up to near the end of their shelf-lives. No clear

trends or changes were observed. Based on the in-use stability results no separate in-use shelf life is deemed necessary for the product in the product information.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Entecavir Xiromed 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 Xiromed 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

The MAH conducted a bioequivalence study in which the pharmacokinetic profile of the test product Entecavir Xiromed 1 mg film-coated tablets (Medical Valley Invest AB, Sweden) is compared with the pharmacokinetic profile of the reference product Baraclude 1 mg film-coated tablets (Bristol Myers Squibb Pharma EEIG, United Kingdom).

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 has requested a biowaiver for the lower strength Entecavir Xiromed 0,5 mg film-coated tablets based on the bioequivalence study with the 1 mg formulation. All biowaiver requirements are fulfilled:

- The qualitative and quantitative composition of the different strengths is dose proportional and only differs in the used film coating, which is acceptable and in accordance with the guideline.
- Both Entecavir Xiromed strengths are manufactured by the same process.
- Both tablets also have comparable dissolution profiles according to the provided *in vitro* dissolution data

Bioequivalence study

Design

A randomised, open label, two treatment, single period, single dose, parallel design bioequivalence study was carried out under fasted conditions in 60 healthy male subjects, aged 19-43 years. An equal amount of subjects (n=30) received the test formulation compared to the reference formulation. The tablet was orally administered with 240 ml water after an overnight. There was one dosing period.

Blood samples were collected at 0.17, 0.33, 0.50, 0.67, 0.83, 1.00, 1.25, 1.50, 1.75, 2.0, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, 48 and 72 hours after administration of the products.

Although not recommended by the guideline on bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1) a parallel study design has been chosen, because of the long half life (terminal elimination half life of 128 - 149 hours) of the drug. The population is chosen in accordance with the guideline. The method of randomisation was acceptable. The sampling period is in accordance with the guideline on the investigation of bioequivalence and considered acceptable to estimate pharmacokinetic parameters. The concentration of the parent

compound entecavir was determined in plasma, which is appropriate. The study is conducted under fasting conditions, which is in accordance with the product specific guidance. The design of the study is acceptable.

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
All subjects were eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of entecavir monohydrate under fasted conditions.

Treatment N=30 for each group	**AUC_{0-t} (ng.h/ml)**	**C_{max} (ng/ml)**	**t_{max} (h)**
Test	26.74 ±4.13	9.63 ±2.58	0.67 (0.50 - 1.50)
Reference	27.30 ±3.99	9.90 ±1.64	0.67 (0.50 - 2.00)
***Ratio (90% CI)**	0.98 (0.92 - 1.05)	0.95 (0.87 - 1.05)	--
CV (%)	14.40	22.21	--
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			

**ln-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 Xiromed 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 Xiromed.

Table 2. Summary table of safety concerns as approved in RMP

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
Missing information	• Long term safety and clinical outcomes data • Use in the paediatric population • Use in pregnancy • Use in elderly patients (≥65 years pf 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

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 the PL content of Baraclude 0.5 mg film-coated tablets and the PL layout of Levetiracetam Hetero 750 mg film-coated tablets (PT/H/515/001-004/DC). 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 Xiromed 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 Xiromed with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 15 May 2019.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse