20 July 2017
EMA/520001/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Entecavir Accord

International non-proprietary name: entecavir

Procedure No. EMEA/H/C/004458/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Table of contents

List of abbreviations

AAS	Atomic Absorption Spectrometry
ABC	(1S,2S,3S,5S)-5-(2-Amino-6-(benzyloxy)-9Hpurin-9-yl)-3-(benzyloxy)-2-(benzyloxymethyl) Cyclopentanol
AE	Adverse Event
Alu	Aluminium
ANOVA	Analysis of Variance
API	Active Pharmaceutical Ingredient
ASMF	Active Substance Master File
AUC ratio	The ratio of AUC_{0-t} to $AUC_{0-\infty}$ expressed in (%) percentage
AUC_{0-72}	The area under the plasma concentration *versus* time curve from time 0 to 72 hours
$AUC_{0-\infty}$	The area under the plasma concentration *versus* time curve from time 0 to infinity
AUC_{0-t}	The area under Plasma concentration *versus* time curve from time 0 to t, where t = time of last measurable concentration
BBO	(1S,2R,3S,5R)-3-(benzyloxy)-2-(benzyloxymethyl)-6-oxabicyclo[3.1.0] hexane
BIA	7-(benzyloxy)-3H-imidazo[4,5-b]pyridin-5-amine
BMC	(1S,2S,3S,5S)-3-(benzyloxy)-5-(6-(benzyloxy)-2-((4-methoxyphenyl) diphenyl methylamino)-9H purin-9-yl)-2-(benzyloxymethyl) Cyclopentanol
BMD	1. 6-(Benzyloxy)-9-((1S,3R,4S)-4-(benzyloxy)-3-benzyloxy methyl)-2-Methylene cyclopentyl)-N-((4-methoxy phenyl) diphenyl methyl)-9H-Purine-2-Amine
BMI	Body Mass Index
CC	Calibration curve
CFU	Colony-forming unit
C_{max}	Maximum measured plasma concentration over the time span specified
CoA	Certificate of analysis
CRC	Clinical Research Centre
CV	Captured volume
CV%	Percentage Coefficient of Variation
DSC	Differential scanning calorimetry
EC	Ethics Committee
EC	European Commission
EEA	European Economic Area
ER	Environmental Risk
ERA	Environmental Risk Assessment
ETV	Entecavir monohydrate
ETV-I	2-Amino-9-((1S,3R,4S)-4-(benzyloxy)-3-(benzyloxymethyl)-2-methylenecyclopentyl)-9H-purin-6-ol
ETV-II	Entecavir monohydrate (pure-wet)
ETV-II	Entecavir monohydrate (pure-dry)
EU	European Union
f2	The similarity factor
FT-IR	Fourier Transform Infrared Spectroscopy
GC	Gas chromatography
GCP	Good Clinical Practice
GLM	General Linear Models
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HCl	Hydrochloric Acid
HDPE	High Density Polyethylene
H-ETVRC01	2-Amino-9-((1S,3R,4S)-3-(benzyloxymethyl)-4-hydroxy-2- methylenecyclopentyl)-9H-purin-6-ol
H-ETVRC02	2-Amino-9-((1S,3R,4S)-4-(benzyloxy)-3[(benzyloxy)methyl]-2-methylenecyclopentyl)-9H-6-purinol
HPLC	High Performance Liquid Chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

ICMR	Indian Council of Medical Research
ID	Identification
IPC	In-process controls
IR	Infra-Red Spectroscopy
ISR	Incurred Sample Reanalysis
K_{el}	Apparent first – order terminal elimination rate constant
KF	Karl Fischer
kg/m^2	Kilogram per square meter
LOD	Limit of detection
LOQ	Limit of quantitation
LQCT	Last measurable blood sampling point
LSM	Least Square Mean
MAH	Marketing Authorisation Holder
mg	Milligram
min	Minute
Ml	Milliliter
MS	Mass Spectrometry
MTC	4-Methoxy trityl chloride
N	Number of subjects
ng	Nanogram
NKEL	Number of points used in calculation of terminal elimination rate constant
NLT	Not Less Than
NMR	Nuclear Magnetic Resonance
NMT	Not More Than
No	Number
ºC	Degree Celsius
OOS	Out of specification
Ph.Eur.	European Pharmacopoeia
QCs	Quality Control Sample
QP	Qualified Person
RH	Relative Humidity
rpm	Revolutions per minute
SAS	Statistical Analysis Software
SmPC, SPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
$T_{1/2}$	Apparent first-order terminal elimination half-life calculated as $0.693/K_{el}$
TGA	Thermo-Gravimetric Analysis
TLIN	Time point at which log linear elimination begins
T_{max}	Time of the maximum measured plasma concentration
USP	United States Pharmacopoeia
UV	Ultraviolet light
WFI	Water for injections
pXRD	Powder X-ray diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Accord Healthcare Ltd submitted on 1 July 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Entecavir Accord, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a Centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 26 May 2016.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product, as defined in Article 10 (2)(a) of Directive 2001/83/EC, for which a marketing authorisation is or has been granted in in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indications:

Entecavir Accord is indicated for the 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.

Entecavir Accord is also indicated for the 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.

The legal basis for this application refers to:

Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information, complete quality data and a bioequivalence study with the reference medicinal product Baraclude 1 mg film-coated tablets instead of non-clinical and clinical unless justified otherwise .

The chosen reference product is:

Medicinal product which is or has been authorised in accordance with Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Baraclude 0.5 mg film-coated tablets
- Marketing authorisation holder: Bristol-Myers Squibb Pharma EEIG
- Date of authorisation: 26/06/2006
- Marketing authorisation granted by:

  - Community
- Community Marketing authorisation number: EU/1/06/343/001, 003, 006
- Product name, strength, pharmaceutical form: Baraclude 1 mg film-coated tablets
- Marketing authorisation holder: Bristol-Myers Squibb Pharma EEIG
- Date of authorisation: 26/06/2006
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/06/343/002, 004, 007

Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Baraclude 0.5 mg film-coated tablets
- Marketing authorisation holder: Bristol-Myers Squibb Pharma EEIG
- Date of authorisation: 26/06/2006
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/06/343/001, 003, 006

- Product name, strength, pharmaceutical form: Baraclude 1 mg film-coated tablets
- Marketing authorisation holder: Bristol-Myers Squibb Pharma EEIG
- Date of authorisation: 26/06/2006
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/06/343/002, 004, 007

Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Product name, strength, pharmaceutical form: Baraclude 1 mg film-coated tablets
- Marketing authorisation holder: Bristol-Myers Squibb Pharma EEIG
- Date of authorisation: 26/06/2006
- Marketing authorisation granted by:
  - Community
- Community Marketing authorisation number: EU/1/06/343/002, 004, 007
- Bioavailability study number(s): 3074/13

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Ewa Balkowiec Iskra

- The application was received by the EMA on 1 July 2016.
- The procedure started on 18 August 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 04 November 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 15 November 2016.
- During the meeting on 15 December 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 20 April 2017
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 29 May 2017.
- During the PRAC meeting on 09 June 2017, the PRAC agreed on a PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 22 June 2017, the CHMP agreed on a list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 27 June 2017.
- During the meeting on 20 July 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing authorisation to Entecavir Accord.

2. Scientific discussion

2.1. Introduction

The application for Entecavir Accord was submitted by Accord Healthcare Ltd, via the centralised procedure as a Generic of a Centrally Authorised Medicinal Product of Regulation (EC) No 726/2004 and according to Article 10(1) generic application of Directive 2001/83/EC. Entecavir Mylan is a generic version of the already approved reference product Baraclude 0.5 mg film-coated tablet, authorized on 26 June 2006 (marketing authorisation numbers EU/1/06/343/003, EU/1/06/343/006 and EU/1/06/343/001) and to Baraclude 1 mg film-coated tablet, authorized on 26 June 2006 (marketing authorisation numbers EU/1/06/343/004, EU/1/06/343/007 and EU/1/06/343/002).

Entecavir is a guanosine nucleoside analogue with activity against hepatitis B virus (HBV) polymerase. After phosphorylation to the tri-phosphate (TP) form, entecavir-TP, by competing with the natural substrate deoxyguanosine TP, functionally inhibits the 3 activities of the viral polymerase: (1) priming of the HBV polymerase, (2) reverse transcription of the negative strand DNA from the pregenomic messenger RNA, and (3) synthesis of the positive strand HBV DNA. In conclusion, entecavir inhibits HBV DNA synthesis.

The applicant submitted one bioequivalence study conducted with Entecavir Accord 1 mg, and a biowaiver for the 0.5 mg was claimed.

Entecavir Accord is indicated for the treatment of chronic hepatitis B virus (HBV) infection in adults with (1) 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 as well as with (2) decompensated liver disease, for both compensated and decompensated liver disease.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 0.5 mg or 1 mg of entecavir (as monohydrate) as active substance.

Other ingredients in the tablet cores are: calcium carbonate, pregelatinized starch, carmellose sodium, soy polysaccharides, citric acid monohydrate, sodium stearyl fumarate.

The film-coating contains: hypromellose, titanium dioxide (E171), macrogol, polysorbate 80 *[0.5 mg]* or hypromellose, titanium dioxide (E171), macrogol, iron oxide red (E172) *[1 mg]*.

The product is available in pack sizes of 30 or 90 tablets in Alu/Alu perforated unit dose blisters or 30 tablets in high-density polyethylene (HDPE) bottles as described in section 6.5 of the SmPC.

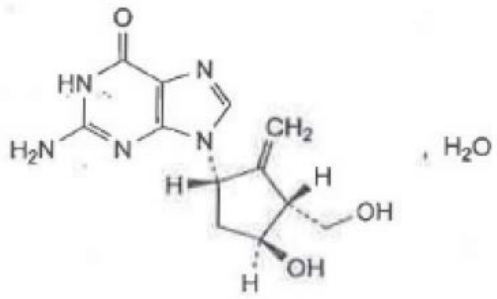
2.2.2. Active substance

Entecavir monohydrate is the subject of a monograph in the European Pharmacopoeia. The commercial manufacturing process consistently results in entecavir monohydrate crystalline form. The active substance master file (ASMF) procedure was followed to provide the information on the active substance. The current version of ASMF is in line with Ph. Eur. monograph of entecavir monohydrate.

General information

The chemical name of entecavir monohydrate is 2-Amino-9-[(1S,3R,4S)-4-hydroxy-3-(hydroxymethyl)-2-methylidenecyclopentyl]-1,9-dihydro-6H-purin-6-one monohydrate corresponding to the molecular formula $C_{12}H_{15}N_5O_{3,}H_20$ and has a relative molecular mass 295.3 and has the following structure:

Figure 1. Structure of entecavir monohydrate



The active substance is white to off-white powder; it is non-hygroscopic and insoluble in water.

The structure of the active substance was confirmed by elemental analysis, UV, FT-IR, ^{1}H-NMR, ^{13}C-NMR and mass spectrometry techniques and supplemented with physicochemical tests for specific optical rotation, polymorphism, solubility, pKa and pH.

Entecavir monohydrate exhibits stereoisomerism due to the presence of three chiral centres. The intended isomer has (1S,3R,4S) configuration. The enantiomeric purity of entecavir monohydrate is obtained by controlling the enantiomeric purity of the starting material (N3) by 'chiral HPLC method' and is routinely checked by specific optical rotation test in the active substance specification. In addition the six diastereomers of entecavir monohydrate are routinely controlled in the active substance specifications as unspecified impurities using a HPLC method.

Polymorphism has been observed for entecavir monohydrate. Three crystalline polymorphic forms are described in the literature; monohydrate (prepared using water as solvent), N-2 (prepared using anhydrous methanol as solvent) and IP.3-4 (prepared using isopropanol as solvent). It has been confirmed via TGA and pXRD studies that the commercial manufacturing process consistently results in entecavir monohydrate crystalline form and it has been demonstrated that there is no change in the polymorphic form during the active substance stability studies. In addition, it has been demonstrated that the polymorphic form does not change during finished product manufacture or storage. Entecavir crystalline monohydrate form is the same polymorphic form as used in the reference product. A test for confirming the polymorphic form via pXRD is included in the active substance specification.

Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Entecavir monohydrate is synthesized in five main synthetic steps using well defined starting materials with acceptable specifications. Following the synthesis and purification steps the active substance is dried and sieved prior to packaging. During the procedure the originally proposed starting materials were not deemed to be acceptable. These concerns were addressed by the applicant by redefinition of the starting materials to an earlier point in the synthesis, with appropriate specifications set for these materials and

the introduction of appropriate additional intermediate specifications. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities including process impurities, degradants, isomeric, inorganic, solvent and genotoxic impurities were well discussed with regards to their origin and characterised.

The active substance is packaged in polythene bags which comply with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification complies with the Ph. Eur monograph for entecavir monohydrate and includes tests for appearance, solubility, identification (IR, HPLC, pXRD), water content (KF), specific optical rotation (Ph. Eur.), sulfated ash (Ph. Eur.), related compounds (HPLC), assay (HPLC), residual solvents (GC), microbiological examination (Ph. Eur.) and particle size (laser diffraction).

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data on three commercial batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on three commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for 36 months under long term conditions at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided.

The following parameters were tested: appearance, identification, pXRD, water content, related substances and assay. The analytical methods used were the same as for release and were stability indicating. All tested parameters were within the specifications and did not show any fluctuations or trends.

Data from photostability testing following the ICH guideline Q1B and forced degradation studies under various stress conditions were also provided. The forced degradation studies were carried out with entecavir monohydrate in solid state under ambient, thermal humidity and photolytic conditions and in liquid state under water hydrolysis, acid and base hydrolysis and oxidation conditions. The degradation studies of entecavir monohydrate indicate that the compound is stable upon exposure to ambient, humidity and photolytic stress conditions. Significant degradation was observed upon exposure to thermal stress condition. No significant degradation was observed upon exposure to water hydrolysis. Mild degradation was observed upon exposure to acid hydrolysis. Significant degradation was observed upon exposure to base hydrolysis and oxidation stress condition.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 48 months when stored below 25ºC in a polyethylene bag in a HDPE drum.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

Entecavir 0.5 mg film-coated tablets are presented as white to off white, triangle shaped, biconvex film-coated tablets debossed with ‘J' on one side and ‘110’ on other side; 8.55 x 8.25 mm (approx.).

Entecavir 1 mg film-coated tablets are presented as pink, triangle shaped, biconvex film - coated tablets debossed with 'J' on one side and '111' on other side; 10.82 x 10.45 mm (approx.). They are available in pack sizes of 30 or 90 tablets in Alu/Alu perforated unit dose blisters or high-density polyethylene (HDPE) bottles as described in section 6.5 of the SmPC.

The majority of excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards, where applicable. There are no novel excipients used in the finished product formulation. Following questions raised during the procedure the applicant provided updated specifications for the non-pharmacopoeial excipient, soy polysaccharides. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The aim of the pharmaceutical development was to develop generic entecavir tablets at the strength of 0.5 mg and 1 mg to be bioequivalent to the commercial reference product Baraclude® (Entecavir) 0.5 mg and 1 mg tablets, and which had acceptable physiochemical properties, stability, and ease of manufacture.

Entecavir monohydrate of consistent particle size distribution was used throughout the product developmental batches. These particle size limits will be applied to entecavir monohydrate to be used in commercial manufacture as per the active substance specification.

Compatibility studies between the active substance and excipients were performed and only excipients found to be compatible with the active substance were selected for the final formulation.

Six different formulations with differing qualitative and quantitative compositions were investigated during the product development, with consequential updates to the manufacturing process. The appearance, assay, related compounds, disintegration, dissolution, hardness, friability, uniformity of weight of the resulting tablets were monitored. The finally chosen formulation was subjected to accelerated and stress stability studies.

The finally chosen formulation used in the bioequivalence study and proposed for commercialisation has a different qualitative composition to that of the reference product.

Table 1. Comparison of test and reference product composition

Entecavir Accord 1 mg film-coated tablets	Baraclude 1 mg film-coated tablets
Tablet core: Calcium carbonate Starch, Pregelatinized Carmellose sodium Soy polysaccharides Citric acid monohydrate Sodium stearyl fumarate	Tablet core: Crospovidone Lactose monohydrate Magnesium stearate Cellulose, Microcrystalline Povidone

Nevertheless, an in-vivo bioequivalence study comparing Entecavir 1 mg film-coated tablets and Baraclude® 1 mg tablets was performed and the products were demonstrated to be bioequivalent. Comparative dissolution studies of the test and reference products and different strengths of test product were carried out across the normal physiological pH range (in 0.1 N HCl, pH 4.5 acetate buffer, pH 6.8 phosphate buffer). A biowaiver was granted for the Entecavir 0.5 mg film-coated tablets as it met the conditions outlined in the CHMP guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1). The discriminatory power of the QC dissolution test method has been demonstrated. The limits for the QC dissolution test in the finished product specification have been set, taking account of the biobatch dissolution results, to NLT 85% (Q) in 15 minutes.

The primary packaging is Alu/Alu perforated unit dose blisters or high-density polyethylene (HDPE) bottle with child resistant polypropylene closure. The materials comply with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of eleven steps:

1. Weighing and sifting,
2. Dry mixing,
3. Preparation of drug solution,
4. Wet granulation,
5. Drying,
6. Sifting and milling,
7. Extra granular material sifting
8. Pre-lubrication,
9. Lubrication,
10. Compression,
11. Film-coating.

The process can be considered to be a non-standard manufacturing process due to the active substance content of the tablet being less than 2 %.

The in-process controls and control of intermediate are adequate for this type of manufacturing process / pharmaceutical form. The critical steps in the manufacturing process have been identified as wet granulation, drying, pre-lubrication, lubrication and compression. The holding times and packaging storage conditions of different intermediates between the process steps have been specified and hold time study protocol has been attached and considered acceptable.

The manufacturing process has been validated by studies on three consecutive full-scale batches of each strength manufactured from common blend at the proposed manufacturing site. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Product specification

The finished product specifications include appropriate tests for this kind of dosage form; description, identification (HPLC, UV), average weight, water content (KF), dissolution (Ph. Eur.), uniformity of dosage units (Ph. Eur.), related compounds (HPLC), assay (HPLC), microbiological examination (Ph. Eur.), identification of colourants.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented. The finished product is released on the market (based on the above release specifications, through traditional final product release testing.

Batch analysis results are provided for three production scale batches of each strength confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data of three full scale pilot batches of each strength finished product stored under long term conditions for 36 months at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, water content, dissolution, related compounds, assay and microbiological examination. The analytical procedures used are stability indicating. No significant changes or trends were observed.

Two batches were also tested for polymorphic form via pXRD. Based on the results obtained, it is concluded that entecavir monohydrate is stable and maintaining its form consistently on storage.

Two batches were exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. It was concluded that entecavir is photo-stable and no special storage conditions for the finished product are required.

A bulk stability study on two batches was performed at long term conditions for 12 months at 25°C±2°C / 60%±5% RH. No significant changes were observed and a 12 month holding time was accepted.

An in-use stability study was conducted on product stored in HDPE containers at 25°C ± 2°C/60% ± 5% RH for 0, 21 and 33 months. In each case the samples were tested after 0, 30, 60, 90 days of simulated use. The results support the proposed in-use shelf life of 90 days.

Based on available stability data, the proposed shelf-life of 3 years without any special storage conditions, with an in-use shelf-life of 90 days, as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, and pharmaceutical aspects

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

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

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. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies are required.

2.3.2. Ecotoxicity / environmental risk assessment

No Environmental Risk Assessment was submitted. This was justified by the applicant as the introduction of Entecavir Accord manufactured by Accord Healthcare Ltd is considered unlikely to result in any significant increase in the combined sales volumes for all entecavir containing products and the exposure of the environment to the active substance. Thus, the ERA is expected to be similar and not increased.

2.3.3. Discussion on non-clinical aspects

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided. This overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. CHMP agreed that no further non-clinical studies are required.

2.3.4. Conclusion on the non-clinical aspects

A summary of the literature with regard to non-clinical data of Entecavir Accord was provided. The non-clinical data for entecavir are well known and thus new non-clinical data are not required. This is in accordance with the relevant guideline and the CHMP considered that additional non clinical studies were not necessary. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for film-coated tablet containing entecavir. To support the marketing authorisation application the applicant conducted one bioequivalence study with an open label, two treatment, single dose, parallel design under fasting / fed conditions. This study was the pivotal study for the assessment.

GCP

The Clinical trial was performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that the clinical trial conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Exemption

A justification for a biowaiver for the lower strength i.e. Entecavir 0.5 mg film-coated tablets has been provided. The Applicant has developed Entecavir film-coated tablets in two different strengths i.e. 0.5 mg and 1 mg for submission in EU. The application for marketing authorisation is based on demonstrating bioequivalence of the test product Entecavir 1mg tablets of Hetero Labs Limited, India with the approved reference product Baraclude (Entecavir) 1 mg tablets of Bristol Myers Squibb Pharma EEIG, United Kingdom.

Justification for requesting biowaiver for the lower strength i.e. Entecavir 0.5 mg film-coated tablets, is prepared according to general biowaiver criteria as specified in the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1 /Corr**. The conditions for waiver of in vivo bioequivalence study with Entecavir 0.5 mg film-coated tablets are listed below:

a. both strengths of Entecavir film coated tablets are manufactured by the same manufacturer at the same manufacturing site using similar manufacturing process.

b. the qualitative composition of both strengths is the same. Entecavir 0.5 mg and 1 mg film coated tablets are direct scale up/scale down formulations.

c. the excipients included in the composition of the formulation are well established and no interaction with the pharmacokinetics of the active substance is expected.

d. entecavir showed linear PK up to a dose of 1.0 mg.

e. the dissolution profiles of both strengths are similar across the pH range of 1.2 to 6.8 i.e. 0.1 N Hydrochloric acid, pH 4.5 Acetate buffer and pH 6.8 Phosphate buffer, both strengths exhibit similar in-vitro performance i.e. greater than 85% release in 15 minutes. The dissolution conditions were appropriate, according to CPMP/EWP/QWP/1401/98 Rev. 1/ Corr** guideline except for the dissolution volume.

Clinical studies

To support the application, the Applicant has submitted one bioequivalence study. The bioequivalence of the test formulation versus the reference product has been investigated on the 1 mg strength (Study 3074/13).

Table 2. Tabular overview of clinical studies

Type of study	Study identifier	Location of study report	Objective(s) of the study	Study Design and Type of control	Test product(s); Dosage regimen; route of administration	Number of subjects	Healthy subjects or diagnosis of patients	Duration Of treatment	Study status; type of report
BE	3074/13	Module 5	Primary objective of this study was to assess the bioequivalence of Entecavir 1 mg tablets of Hetero Labs Limited, India and Baraclude® (Entecavir) 1 mg tablets of Bristol Myers Squibb Pharma EEIG, United Kingdom, in healthy human adult subjects, under fasting conditions.	A randomized, open label, two treatment, Single period, Single dose, parallel design, bioequivalence study in healthy subjects under fasting conditions	One tablet formulation, Single dose, Oral administration	60	Healthy subjects.	A single oral dose of either the test or reference product was administered on one occasion.	Complete abbreviated

2.4.2. Pharmacokinetics

Study 3074/13 - Study Title: A randomized, open label, two treatment, single period, single dose, parallel design, bioequivalence study of Entecavir 1mg tablets of Hetero Labs Limited, India and Baraclude® (Entecavir) 1 mg tablets of Bristol Myers Squibb Pharma EEIG, United Kingdom, in healthy human adult subjects, under fasting conditions.

Methods

Study design

This was an open label, randomized, two treatment, single period, single dose, parallel design, bioequivalence study of Entecavir 1mg tablets of Hetero Labs Limited, India and Baraclude (Entecavir) 1 mg tablets of Bristol Myers Squibb Pharma EEIG, United Kingdom, in healthy human adult subjects, under fasting conditions.

A total of 60 healthy human adult subjects were enrolled and 60 subjects completed the study. The eligible subjects, who fulfilled the study inclusion and exclusion criteria were assigned a sequence number in the order of their presentation for enrolment. Subjects were allocated to treatment groups according to the randomization schedule generated at Lotus Labs Private Ltd. using SAS (version 9.2).

A two arm parallel study design was used with an equal treatment allocation ratio of 1:1 for Entecavir 1mg tablets of Hetero Labs Limited vs. Baraclude (Entecavir) 1 mg tablets. This study was designed and conducted according to assumptions and techniques suitable for bioequivalence studies (open label, randomized, two treatment, single period, single dose, parallel design, bioequivalence study). Sampling of Entecavir was done up to 72.00 hours post dose based on truncated study design as Entecavir has a long terminal elimination half-life.

Test and reference products

Test Product: Entecavir 1mg tablets. Reference Product: Baraclude 1mg film tablets (entecavir). After a supervised overnight fast of at least 10 hours, a single oral dose of the investigational product was administered with 240 mL of water on 15 June 2013 of the study period.

Entecavir Accord 1 mg tablets manufactured by Accord Healthcare Ltd (batch No. ENT21200, manufacturing date 06/2012; exp. date 05/2014) has been compared to Baraclude 1 mg tablets manufactured by Bristol Myers Squibb Pharma EEIG (Batch No: 2B70589, exp. date 07/2013.

Table 3. Identification of Test and Reference Products

	Test Product-T	Reference Product-R
Product	Entecavir 1mg tablets	Baraclude® 1mg film tabletten (entecavir)
Manufacturer	M/S Hetero Labs Limited (Unit-V) APIIC Formulation SEZ Polepally village Jadcherla (Mandal) Mahaboob nagar (District) Pin 509301 Andhra Pradesh India	Bristol Myers Squibb Pharma EEIG Uxbridge Business park Sanderson Road Ux bridge UB8IDH Vereingites konigreich
Description*	Pink coloured triangle shaped biconvex unscored tablet engraved as "111" on one side and "J" on another side.	Pink coloured triangle shaped biconvex unscored tablet engraved as "BMS" on one side and "1612" on another side.
Batch No.	ENT212002	2B70589
Batch Size	1,25,000 Tablets	N/AV
Manufacturing Date	06/2012	N/AV
Expiry Date	05/2014	07.2013

Population studied

246 subjects were screened for this study of which 60 subjects were enrolled and randomized to either the test or the reference product in the study period. In the study period, all 60 subjects were administered either of investigational product. Thus, 60 subjects were dosed in the study period and all 60 subjects completed the study. The inclusion and exclusion criteria are acceptable and performed according to the protocol. All subjects are observed and treated according to the same rules. The data from all treated subjects was treated equally.

The sample size calculation for this study was based on the observed pooled coefficient of variation (CV) for Entecavir as obtained from the sponsor's in-house study data – maximum of Cmax of Entecavir was estimated ~24%. Thus, with the expected CV not exceeding 25% and assuming the true ratio of Cmax and AUC falling within 95% to 105% (5% treatment difference), the study should have 28 evaluable subjects per treatment arm (statistical assumptions: power>80%, α=0.05). Total of 56 evaluable subjects were required for the assessment of bioequivalence. Further, expecting certain dropouts and/or withdrawals in the study, 2 additional subjects were planned to be included in each treatment arm and consequently a total of 4 subjects were considered towards dropouts &/or withdrawals in the study. Thus, a total of 60 subjects were sufficient for this study.

Analytical methods

A sensitive and selective LC-MS/MS method to quantitate Entecavir in K2EDTA human plasma over the concentration range 0.057 ng/mL to 20.594 ng/mL was developed and validated. Entecavir was selectively isolated from 200 µl plasma by solid phase extraction using Strata-X 30 rng/rnL cartridge. Estimation was done by mass spectrometric method, chromatographed on a Atlantis® HILIC SILICA,150 nun x 4.6 mm, 3 µm column.

The analytical method for the determination of Entecavir in human plasma seems to be described adequately; the validations were performed according to the requirements of the EMA “Guideline on bioanalytical method validation” (EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2**)”. Acceptance criteria are in a plausible range.

The analytical portion of the bioequivalence Study No. 3074/13 was adequately conducted according to a validated method (AL-M415-00) and EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2** guideline on an API 4000 detector (Applied Biosystems) using lamivudine as internal standards (IS).

Pharmacokinetic variables

Primary Parameters: AUC0-72 (the area under the plasma concentration versus time curve from time 0 to 72 hours. The parameter will be calculated using linear up/ log down trapezoidal method) and Cmax (maximum observed concentration).

The bioequivalence criteria were based on the 90% Confidence Intervals (CI) of the above parameters.

Secondary Parameters: Tmax, Kel and T½.

Statistical methods

The following summary statistics for the pharmacokinetic parameters was calculated for both the Test (T) and Reference (R) products: Number of observations, arithmetic mean, standard deviation, coefficient of variation (CV %), minimum, median, maximum and geometric mean.

For primary endpoint the log-transformed pharmacokinetic parameters (AUC0-72 and Cmax) were analyzed using General Linear Model (PROC GLM procedure) of SAS. The ANOVA model included treatment as fixed effect. The treatment effect was tested the 5% level of significance using the residual error (mean square error) from the ANOVA, as error term in the F-ratio for the main effect.

The ratio of the Test and Reference product averages (Least Square Means) was estimated for the differences in the Least Square Means (LSM) of the log-transformed data then taking the anti-log of the estimates. Consistent with Schuirmann’s two one-sided tests procedure for bioequivalence, the 90% confidence interval for the ratio of the Test and Reference was estimated using the difference of least square mean between test and reference (estimate), the ‘t’ value at Mean Square Error Degrees of Freedom (df) and the Standard Error of Estimate. The Standard Error of Estimate was calculated using the Mean Square Error and the number of reference subjects from the GLM - ANOVA Model.

The following standards for bioequivalence were applied: 90% confidence interval of the relative mean AUC0-72 and Cmax of the test and reference product should be in a range 80.00% - 125.00% for log-transformed data. For secondary endpoint (analysis of Tmax) Wilcoxon Rank Sum Test was used. The study was implemented by missing data handling technique. For secondary endpoint (Tmax) evaluation Wilcoxon Rank Sum Test was used.

The statistical methodology used in the study is justified and consistent with the principles of guidelines on the investigation of bioequivalence.

Results

The mean (±SD) AUC0-72 for the test product (T) was 26.74 ±4.130 ng.h/mL and for the reference product (R) was 27.30 ± 3.988 ng.h/mL. The mean (±SD) Cmax for the test product (T) and reference product (R) were 9.63 ± 2.578 ng/mL and 9.90 ± 1.640 ng/mL, respectively. The mean Tmax for the test

product (T) and reference product (R) were found to be 0.68 h and 0.82 h, respectively. The mean T1/2 for the test product (T) was 63.64 h and for the reference product (R) was 50.11 h. The mean Kel was 0.02 h-1 and 0.02 h-1 for the test product (T) and the reference product (R) respectively. No values of Kel and T1/2 were reported for Subject no (s). 01, 02, 03, 04, 05, 06, 07, 08, 10, 11, 12, 14, 15, 17, 18, 19, 21, 23, 24, 25, 26, 27, 28, 32, 34, 35, 36, 37, 38, 39, 41, 43, 44, 45, 46, 48, 49, 50, 51, 52, 54, 55, 56, 57, 58 and 60, since their adjusted coefficient of determination i.e., RSQ_A was less than 0.80. The 90% Confidence Intervals for Entecavir log transformed parameters AUC0-72, and Cmax were 91.94 % to 104.05 % (Ratio = 97.81 %) and 86.75 % to 104.84 % (Ratio = 95.37 %) respectively.

The 90% confidence intervals for ln-transformed pharmacokinetic variables Cmax and AUC0-72 were within the conventional bioequivalence range of 80% to 125%. ANOVA did not detect any statistically significant (p-values > 0.05) difference between treatments for AUC0-72 and Cmax. Any subjects did not reach Cmax at the first sampling time point indicating that sampling time schedule was adequate.

Table 4. Pharmacokinetic parameters for analyte (non-transformed values)

Pharmacokinetic parameter	Test		Reference	
	arithmetic mean	SD	arithmetic mean	SD
$AUC_{(0-72h)}$	26.74	4.130	27.30	3.988
C_{max}	9.63	2.578	9.90	1.640
T_{max}*	0.68	0.193	0.82	0.332

AUC_{0-72h} area under the plasma concentration-time curve from time zero to 72 hours
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
C_{max} maximum plasma concentration
T_{max} time for maximum concentration (* median, range)

Table 5. Statistical analysis for analyte (ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals
$AUC_{(0-72h)}$	97.81	91.94 to 104.05
C_{max}	95.37	86.75 to 104.84

* estimated from the Residual Mean Squares

Safety data

Both medicinal products used in this study were found to be safe and well tolerated. There were no serious adverse events (AEs) reported in this study.

One AE reported during the study that occurred following administration of test product T and was considered as related to the investigational product; this AE was itching. It was mild in intensity, treated appropriately and resolved without sequel. The adverse event was not life threatening or required the subject to be hospitalized.

There were 9 cases of increased lactate concentrations (5 after test product and 4 after reference product administration) and 2 cases of higher potassium levels (all cases after test product). In the follow-up the abnormal laboratory values were within reference range in all cases.

Additional data

In vitro dissolution tests

The Applicant has performed in vitro dissolution tests comparing the test and reference bio-batches used in bioequivalence study (Test: Entecavir Tablets 1mg, Batch No.: ENT212002; Reference: Baraclude Tablets 1 mg, 2B70589 as well as with the lower strength of the applied product: Entecavir Tablets 0.5 mg, Batch No.: ENT112002.

a. In vitro dissolution tests complementary to the bioequivalence study

More than 85% of the labelled amount of the drug was released within 15 minutes from both the formulations (the batches used in bioequivalence study) in all the three mediums 0.1N Hydrochloric acid, pH 4.5 Acetate buffer and pH 6.8 Phosphate buffer. Hence, the dissolution profiles can be considered as similar without further mathematical calculations.

b. In vitro dissolution tests in support of bio-waiver

The results of in vitro dissolution tests at three different buffers are reported. The sampling time points (10, 15, 20, 30 and 45 min) are sufficient. 12 units of the product, each tested batch were used. Bearing in mind that more than 85% of the labelled amount of the drug was released within 15 minutes from each tested formulations (all the batches) in all three mediums: 0.1N Hydrochloric acid, pH 4.5 acetate buffer and pH 6.8 phosphate buffer, the dissolution profiles can be considered as similar without further mathematical calculations.

The dissolution conditions were appropriate, according to CPMP/EWP/QWP/1401/98 Rev. 1/ Corr ** except for the dissolution volume. The recommended volume of dissolution medium should be 900 ml or less. However, due to entecavir (1mg) is fully soluble in all the physiological dissolution media tested (solubility > 1mg/1ml of media), the difference between 900ml and 1000ml in this particular case is not expected to modify the profiles which exhibit all >85% dissolved in 15min .

The results of Study 3074/13 with 1 mg formulation can be extrapolated to other strength 0.5 mg.

Conclusions

Based on the presented bioequivalence study Entecavir Accord is considered bioequivalent with Baraclude.

The results of study 3074/13 with 1 mg formulation can be extrapolated to other strengths 0.5 mg, according to conditions in the Guidelines.

2.4.3. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application.

2.4.4. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.5. Discussion on clinical aspects

To support the application, the Applicant has submitted one bioequivalence study. The bioequivalence of the test formulation versus the reference product has been investigated for the 1 mg strength (Study 3074/13). This was an open label, randomized, two treatment, single period, single dose, parallel design, bioequivalence study of Entecavir 1mg tablets of Hetero Labs Limited, India and Baraclude (Entecavir) 1 mg tablets of Bristol Myers Squibb Pharma EEIG, United Kingdom, in healthy human adult subjects, under fasting conditions.

246 subjects were screened for this study of which 60 subjects were enrolled and randomized to either the test or the reference product during the study period. The screening was performed over 21 days as a part of general screening to include subjects for scheduled studies. In the study period, all 60 subjects completed the study and were dosed with either of investigational product. Pharmacokinetic and statistical analyses were performed on data from all 60 subjects.

Sample size was estimated based on appropriate methodology and with adequate statistical assumptions. All statistical analyses were conducted with data from 60 subjects.

The study was planned to minimise the variability of all factors involved except that of the products being tested. The inclusion and exclusion criteria are acceptable and were according to the protocol. All subjects are observed and treated according to the same rules. The data from all treated subjects was treated equally.

As a bioequivalence study should in general be conducted at the highest strength, the highest strength proposed for approval was administered (since bioequivalence at lower strengths was not needed to be established, as per regulatory acceptance criteria). Therefore, Entecavir 1mg was chosen to achieve sufficient analyte plasma levels to characterize the pharmacokinetic profile. The subjects were administered a single oral dose of 1 mg of Entecavir of either the test or reference product in the single period of the study. According to Guidance on the investigation of bioavailability and bioequivalence (CPMP/EWP/QWP/1401/98), if several strengths of a test product are applied for, it may be sufficient to establish bioequivalence at only one or two strengths depending on the proportionality in composition between the different strengths. The dosage of 1 mg of Entecavir was reported to exhibit linear pharmacokinetics up to the dose of 1mg after oral administration. Other required criteria: i) the pharmaceutical products are manufactured by the same manufacturing process, ii) the qualitative composition of the different strengths is the same, iii) the composition of the strengths are quantitatively proportional have also been met.

The Applicant has performed in vitro dissolution tests comparing the test and reference bio-batches used in bioequivalence study (Entecavir Tablets 1mg and Baraclude Tablets 1 mg, as well as with the lower strength of the applied product: Entecavir Tablets 0.5 mg). More than 85% of the labelled amount of the drug was released within 15 minutes from both the formulations in all the three mediums 0.1N Hydrochloric acid, pH 4.5 Acetate buffer and pH 6.8 Phosphate buffer. Hence, the dissolution profiles can be considered as similar without further mathematical calculations. However, the dissolution conditions used in the dissolution tests were not fully adequate due to the inappropriate dissolution volume, which was 1000ml, instead 900ml or less, according to CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **. However, due to entecavir (1mg) being fully soluble in all the physiological dissolution media tested (solubility > 1mg/1ml of media), the difference between 900ml and 1000ml in this particular case is not expected to modify the profiles which exhibit all >85% dissolved in 15min. Therefore, the results of Study 3074/13 with 1 mg formulation can be extrapolated to other strength 0.5 mg.

A sensitive and selective LC-MS/MS method to assess Entecavir in K2EDTA human plasma over the concentration range 0.057 ng/mL to 20.594 ng/mL was developed and validated. The methods used for

the determination of the entecavir in K2EDTA human plasma seem appropriate for their purpose, and were adequately validated. The analytical portion of the bioequivalence Study No. 3074/13 was adequately conducted according to a validated method (AL-M415-00) and EMEA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2** guideline on an API 4000 detector (Applied Biosystems) using lamivudine as internal standards (IS).

A two arm parallel study design was used with an equal treatment allocation ratio of 1:1 for Entecavir 1mg tablets of Hetero Labs Limited vs Baraclude (Entecavir) 1 mg tablets. Various pharmacokinetic parameters Cmax, AUC0-72h, Tmax, T1/2, Kel and AUC_%Extrap_obs for Entecavir were calculated. The primary pharmacokinetic parameters determined for test and reference products were: AUC0-72 as well as Cmax. In studies with a sampling period of 72 h, and where the concentration at 72 h is quantifiable, it is sufficient to report AUC truncated at 72h, AUC0-72h. The bioequivalence criteria were based on the 90% Confidence Intervals (CI) of the above parameters. The secondary pharmacokinetic parameters were: Tmax; Kel and T½. Acceptance range for bioequivalence is 80.00%-125.00% for 90% confidence intervals of the geometric least square means ratio for Cmax and AUC0-72h of Entecavir.

Study results submitted by the applicant include statistical analysis appropriate to bioequivalence studies (ANOVA model building and Schiurmann two one sided tests). Analysis of variance was carried out for ln-transformed Cmax, AUC0-72 using PROC GLM procedure. ANOVA model included fixed effect of treatment at the α=0.05 level of significance using the residual error (mean square error) from the ANOVA, as error term in the F-ratio for the main effect. Analysis showed that treatment effect was not significant. The following standards for bioequivalence were applied: 90% confidence interval of the relative mean AUC0-72 and Cmax of the test and reference product should be at least 80.00% and not more than 125.00% for log-transformed data. The 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range.

For secondary endpoint (Tmax) evaluation Wilcoxon Rank Sum Test was used. The statistical methodology and study design were conducted according to recommendations of the EMA Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **). A total of 22 blood samples were collected during the single period. The two 0.0 h blood samples (2 x 4 mL i.e., each 4 mL blood sample was transferred to 2 separate vacutainers) were collected within 1 hour prior to dosing and post dose samples (1 x 4 mL each) 0.167, 0.333, 0.500, 0.667, 0.833, 1.0, 1.25, 1.5, 1.75, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 12.0, 16.0, 24.0, 36.0, 48.0 and 72.0 h in vacutainers containing K2EDTA. The blood sampling points were chosen such that Tmax could be accurately characterized for Entecavir. In addition a sufficient number of samples to adequately describe the plasma concentration-time profile were collected. The sampling schedule included adequately frequent sampling around predicted Tmax to provide a reliable estimate of peak exposure. The sampling schedule covered the plasma concentration time curve long enough to provide a reliable estimate of the extent of exposure.

The mean (±SD) AUC0-72 for the test product was 26.74 ± 4.130 ng.h/mL and for the reference product, it was 27.30 ± 3.988 ng.h/mL. The mean (±SD) Cmax for the test product and reference product were 9.63 ± 2.578 ng/mL and 9.90 ± 1.640 ng/mL respectively. The mean Tmax for the test product and reference product were found to be 0.68 h and 0.82 h respectively. The mean T1/2 for the test product was 63.64 h and for the reference product, it was 50.11 h. The mean Kel was 0.02 h-1 and 0.02 h-1 for the test product and the reference product, respectively. No values of Kel and T1/2 were reported for Subject no (s). 01, 02, 03, 04, 05, 06, 07, 08, 10, 11, 12, 14, 15, 17, 18, 19, 21, 23, 24, 25, 26, 27, 28, 32, 34, 35, 36, 37, 38, 39, 41, 43, 44, 45, 46, 48, 49, 50, 51, 52, 54, 55, 56, 57, 58 and 60, since their adjusted coefficient of determination i.e., RSQ_A was less than 0.80. The 90% Confidence Intervals for Entecavir log transformed parameters AUC0-72, and Cmax were 91.94 % to 104.05 % (Ratio = 97.81 %) and 86.75 % to 104.84 % (Ratio = 95.37 %) respectively.

The 90% confidence intervals for ln-transformed pharmacokinetic variables Cmax and AUC0-72 were within the conventional bioequivalence range of 80% to 125%. ANOVA did not detect any statistically significant (p-values >0.05) difference between treatments for AUC0-72 and Cmax. No subjects reached Cmax at the first sampling time point indicating that sampling time schedule was adequate. Based on the results obtained in the bioequivalence study (Study 3074/13), the Entecavir 1 mg tablets of Hetero Labs Limited, India and Baraclude (Entecavir) 1 mg tablets of Bristol Myers Squibb Pharma EEIG, United Kingdom, in healthy human adult subjects, were judged to be bioequivalent under fasting condition.

Both of investigational products were found to be safe and well tolerated. There were no serious adverse events (AEs) reported in this study. The adverse event was not life threatening or required the subjects to be hospitalized. There were 9 cases of increased lactate concentrations (5 after test product and 4 after reference product administration) and 2 cases of higher potassium levels (all cases after test product) which returned to reference range in all cases in the follow-up.

2.4.6. Conclusions on clinical aspects

A summary of the literature with regard to clinical data of Entecavir Accord was provided and was accepted by the CHMP. This is in accordance with the relevant guideline and additional clinical studies were not considered necessary.

Based on the findings of the submitted bioequivalence study, Entecavir Accord 1 mg Film-coated Tablets (Test) and Baraclude 1 mg Film-coated Tablets (Bristol-Myers Squibb Pharma EEIG) are considered bioequivalent with respect to rate and extent of absorption.

Biowaiver criteria are considered fulfilled and the bioequivalence conclusions can be extended to the 0.5 mg strength.

2.5. Risk management plan

Safety concerns

Important Identified Risk	• Exacerbation of Hepatitis • ETV Resistance • Emergence of resistant HIV in HIV/HBV co infected patients not concurrently receiving effective HIV treatment
Important Potential Risk	• Carcinogenicity • Mitochondrial Toxicity
Missing information	• Long term safety and clinical outcomes data • Use in pregnancy and lactation • Use in elderly patients (≥65 years of age)

	• Use in severe acute exacerbation of CHB • Use in the Paediatric Population

Pharmacovigilance plan

Only routine pharmacovigilance activities are carried out. No additional pharmacovigilance activities are warranted.

Risk minimisation measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Important Identified Risks: Exacerbation of hepatitis	Section 4.4 and 4.8 of proposed SmPC and corresponding section of PIL has information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed
Important Identified Risks: ETV Resistance	Section 4.4 and 5.1 of proposed SmPC and corresponding section of PIL has information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed
Important Identified Risks: Emergence of resistant HIV in HIV/HBV co- infected patients not concurrently receiving effective HIV treatment	Section 4.4, 4.8 and 5.1 of proposed SmPC and corresponding section of PIL has information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed
Important potential risk: Carcinogenicity	Section 5.3 of proposed SmPC has information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important potential risk: Mitochondrial Toxicity	None proposed	None proposed
Missing Information: Long term safety and clinical outcomes data	Section 4.2 and 5.1 of proposed SmPC has information on this safety concern. Routine risk minimisation measures including the prescription only status of the product.	None proposed
Missing Information: Use in pregnancy and lactation	Section 4.6 and 5.3 of proposed SmPC and corresponding section of PIL has information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed
Missing Information: Use in elderly patients (≥65 years of age)	Section 4.2 and 5.2 of proposed SmPC has information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed
Missing Information: Use in severe acute exacerbation of CHB	None proposed	None proposed
Missing Information: Use in Pediatric Population	Section 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of proposed SmPC and corresponding section of PIL has information has information on this safety concern. Other routine risk minimisation measures including the prescription only status of the product.	None proposed

Conclusion

The CHMP and PRAC considered that the risk management plan version 3.0 is acceptable.

2.6. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Product information

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons:

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Baraclude. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-risk balance

This application concerns a generic version of entecavir film-coated tablets. The reference product Baraclude is indicated for treatment of chronic hepatitis B. No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and was considered sufficient. From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

The bioequivalence study forms the pivotal basis with a randomized, open label, two treatment, single period, single dose, parallel design under fasting conditions. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Entecavir Accord met the protocol-defined criteria for bioequivalence when compared with the Baraclude. The point estimates and their 90% confidence intervals for the parameters AUC_{0-t},, $AUC_{0-\infty}$, and C_{max} were all contained within the protocol-defined acceptance range of [range, e.g. 80.00 to 125.00%]. Bioequivalence of the two formulations was demonstrated.

A benefit/risk ratio comparable to the reference product can therefore be concluded.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are

required beyond those included in the product information.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Entecavir Accord is favourable in the following indication:

Entecavir Accord is indicated for the 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.

Entecavir Accord is also indicated for the 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.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.