This part outlines the scientific assessment and knowledge about this product at the time of prequalification. Updates to this information are included in parts 1 to 5 and 8 of this WHOPAR.

SCIENTIFIC DISCUSSION

Name of the Finished Pharmaceutical Product	[HP035 trade name]*
Manufacturer of Prequalified Product	RV Lifesciences Limited
Active Pharmaceutical Ingredient(s) (API)	Entecavir (monohydrate)
Pharmaco-therapeutic group (ATC Code)	J05AF10
Therapeutic indication	[HP035 trade name] is indicated for the treatment of chronic hepatitis B virus (HBV) infection

1. Introduction

[HP035 trade name] is indicated for the treatment of chronic hepatitis B virus (HBV) infection with any of the following features:

- Significant fibrosis or cirrhosis based on clinical criteria;
- Hepatitis B virus DNA exceeding 2000 units/mL and alanine aminotransferase (ALT) level above the upper limit of normal (ULN) *or*, if HBV DNA assay is not available, persistently raised ALT levels over 6 to 12 months;
- Presence of co-infections (such as HIV infection, hepatitis C or D); a family history of liver cancer or cirrhosis; immune suppression; comorbidities (such as diabetes, liver steatosis); or extrahepatic manifestations of HBV infection (such as glomerulonephritis or vasculitis).

[HP035 trade name] should be initiated by a health care provider experienced in the management of chronic hepatitis B virus.

2. Assessment of quality

The assessment was done in accordance with the requirements of WHO's *Guidelines on submission of documentation for a multisource (generic) finished pharmaceutical product for the WHO Prequalification of Medicines Programme: quality part*.

Active pharmaceutical Ingredient (API)

A CEP (Certificate of Suitability) issued by the EDQM was submitted for entecavir monohydrate ensuring good manufacturing control and applicability of the respective Ph. Eur monograph to control the quality of the API.

Other ingredients

Other ingredients used in the tablet formulation include microcrystalline cellulose, copovidone, crospovidone, lactose monohydrate and magnesium stearate, all being pharmacopoeial controlled. The commercially sourced proprietary film-coating mixture contains hypromellose, titanium dioxide, macrogol/PEG and polysorbate. Lactose monohydrate and magnesium stearate are from bovine and

* Trade names are not prequalified by WHO. This is the national medicines regulatory authority's responsibility.

vegetable origin, respectively. TSE/BSE compliance declarations were provided for the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a white to off-white, round, film-coated tablet. It is biconvex (rounded on top and bottom) with a flat edge. The tablet has 'A' debossed (stamped into) one side and '12' on the other side. The tablets are packaged in either aluminium foil on aluminium foil blister cards or in round, opaque white plastic (HDPE) bottles. Each bottle also contains a sachet of desiccant (drying material). The bottles have aluminium/plastic foil seals and white, childproof plastic (polypropylene) screw caps.

Two strengths of entecavir (as monohydrate) tablets proportionally similar in composition were developed: 1mg and 0.5mg. The development focused on the higher strength, which was used in the BE study against the WHO recommended comparator product Baraclude (Entecavir) 1 mg tablets. Once the formulation for the 1mg strength was finalized, the 0.5mg strength was pursued using dose-proportionality approach.

The aim of the formulation development strategy was to obtain a stable multisource product bioequivalent to the WHO recommended comparator product. The selection of the excipients was primarily based on literature survey, the qualitative composition of the comparator product, previous experience with similar formulations and API-excipient compatibility studies. A wet granulation manufacturing process was selected to achieve the desired blend uniformity as well as content uniformity. Various experiments were performed to select and optimize the concentration of excipients and other process parameters to obtain tablets of desired characteristics, including dissolution profile similarity with the comparator product. Satisfactory in-process controls have been established.

According to a risk evaluation by the applicant, the entecavir tablets have no potential to contain nitrosamine impurities and hence no risk was identified.

Specifications

The finished product specifications include tests for appearance, identification of the API (HPLC and UV), average mass of tablet, uniformity of mass, water content (KF), disintegration time, hardness, dissolution (HPLC detection), assay (HPLC), uniformity of dosage units (content uniformity), related substances (HPLC) and microbial limits. The test procedures have been adequately validated.

Stability testing

Stability studies have been conducted at 30°C/75%RH (zone IVb) as long-term storage conditions and for six months at accelerated conditions in the packaging proposed for marketing of the product. The product proved to be quite stable at these storage conditions, with no significant changes or trends observed. Based on the available stability data, the proposed shelf life and storage conditions as stated in the SmPC are acceptable. The in-use storage periods after first opening of the bottles are based on in-use stability data.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2023 according to internationally accepted guidelines.

An open-label, balanced, randomized, two treatment, two sequence, two period, two way cross-over, single oral dose bioequivalence study of Entecavir tablets 1 mg of RV Lifesciences Limited, India and Baraclude (entecavir tablets) 1 mg of Bristol-Myers Squibb Pharma, Ireland in normal, healthy, adult, human subjects under fasting condition (study no. BE/22/289).

The objective of the study was to compare the bioavailability of the stated Entecavir 1 mg tablet manufactured by/for RV Lifesciences Limited, India (test drug) with the reference formulation Baraclude® 1 mg tablet (Bristol-Myers Squibb Pharma) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, crossover study in healthy subjects under fasting conditions. Each subject was assigned to receive each of the following two treatments in a randomized fashion:

Treatment T: Test – 1 tablet Entecavir 1 mg

(entecavir 1 mg)
Batch no. RV22093.

Treatment R: Reference – 1 tablet Baraclude® 1 mg

(entecavir 1 mg)

Batch no. 8032453.

A 52-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 23 samples within 72h post dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for entecavir were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 0.1 ng/ml for entecavir.

The study was performed with 36 participants; data generated from a total of 34 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

Arithmetic mean and geometric mean values of the pharmacokinetic variables for entecavir as well as statistical results are summarised in the following table:

Entecavir

Pharmacokinetic Parameter	Test formulation (T) arithmetic mean ± SD (*)	Reference (R) arithmetic mean ± SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)#	0.67 (0.34 – 2.34)	0.84 (0.34 – 2.01)	-	-
C_{max} (ng/ml)	10.6 ± 2.7 (10.2)	11.1 ± 2.4 10.9)	94.0	87.2 – 101.4
AUC_{0-t} (ng.h/ml)	29.0 ± 6.4 (28.3)	29.4 ± 6.1 (28.7)	98.3	95.2 – 101.6
AUC_{0-inf} (ng.h/ml)	35.3 ± 8.6	36.1 ± 7.9	-	-

*geometric mean; #median (range)

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding entecavir. Accordingly, the test Entecavir 1 mg tablet meets the criteria for

bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Baraclude® 1 mg tablet (Bristol-Myers Squibb Pharma).

A biowaiver was granted for the additional 0.5 mg tablet strength (RV Lifesciences Limited, India) in accordance to WHO guideline. In comparison with the strength of the test product used in the bioequivalence study, the Entecavir 0.5 mg tablet was determined to be qualitative essential the same, the ratio of active ingredient and excipients between the strengths was considered essential the same and the dissolution profiles between the formulations for the APIs were determined the same.

4. Summary of product safety and efficacy

[HP035 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the comparator product. According to the submitted data on quality and bioavailability, [HP035 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Baraclude® 1 mg tablet (Bristol-Myers Squibb Pharma) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HP035 trade name] is considered acceptable when guidance and restrictions stated in the summary of product characteristics (SmPC) are considered. Refer to the SmPC (WHOPAR part 4) for data on clinical safety.

5. Benefit risk assessment and overall conclusion

Quality

Physicochemical and biological aspects relevant to the uniform pharmaceutical characteristics have been investigated and are controlled in a satisfactory way. The quality of this product is considered to lead to an acceptable clinical performance when [HP035 trade name] is used in accordance with the SmPC.

Bioequivalence

[HP035 trade name] has been shown to be bioequivalent with Baraclude® 1 mg tablet (Bristol-Myers Squibb Pharma) and a biowaiver on the 0.5 mg strength was obtained based on WHO guideline.

Efficacy and Safety

Regarding clinical efficacy and safety, [HP035 trade name] is considered effective and safe to use when the guidance and restrictions in the SmPC are taken into consideration.

Benefit Risk Assessment

Based on WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit–risk profile of [HP035 trade name] was acceptable for the following indication: chronic hepatitis B virus infection, and would allow inclusion of [HP035 trade name], manufactured at RV Lifesciences Limited , Plot No. H-19, MIDC Waluj, Aurangabad 431133, Maharashtra State, India in the list of prequalified medicinal products.