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	[HP002 trade name][*]
Manufacturer of Prequalified Product	Hetero Labs Limited, Unit-V TSIIC Formulation SEZ, Survey No. 439,440,441 & 458 Polepally village, Jadcherla Mandal, Mahaboob Nagar (Dist) – 509301, Telangana, India
Active Pharmaceutical Ingredient(s) (API)	Sofosbuvir
Pharmaco-therapeutic group (ATC Code)	Direct-acting antiviral; ATC code: J05AX15
Therapeutic indication	[HP002 trade name] is indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adults and in adolescents aged 12 to less than 18 years.

1. Introduction

[HP002 trade name] is indicated indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adults and in adolescents aged 12 to less than 18 years. Treatment regimens should follow most recent WHO treatment guidelines, supplemented by other authoritative guidelines.

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*.

Sofosbuvir is a white to off-white powder. It is slightly soluble in water and methanol. Sofosbuvir contains five chiral centres and exhibits isomerism.

The manufacture of the API entails several steps and is well described. The manufacturer consistently produces the crystalline form 6, which is routinely controlled by p-XRD in the specifications of the API.

The API specifications include tests for description, solubility, identification (IR, HPLC and p-XRD), water content (KF), heavy metals, related substances (HPLC), stereochemical purity (HPLC), assay (HPLC), residual solvents (GC), tin content (ICP-MS; ≤ 10ppm), methyl methane sulfonate, ethyl methane sulfonate and isopropyl methane sulfonate content (GC-MS; ≤ 3.75ppm for each) and particle size distribution (PSD). The PSD limits are based on the results obtained for the API batch

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

used in the manufacture of the FPP biobatch. The related substances limits are in accordance with ICH Q3A.

Stability testing was conducted according to the requirements of WHO. The proposed re-test period is justified based on the stability results when the API is stored in the original packing material.

Other ingredients

Other ingredients used in the core tablet formulation include mannitol, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide and magnesium stearate, all being pharmacopoeial controlled. The commercially sourced proprietary film-coating mixture contains polyvinyl alcohol partially hydrolysed, macrogol/polyethylene glycol, talc, titanium dioxide and FD&C yellow #6/ sunset yellow FCF aluminium lake. Magnesium stearate is from plant origin. None of the excipients used in the manufacture of the tablets are of human or animal origin. BSE/TSE compliance declarations were provided for all the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is an orange, oval, film-coated tablet. It is biconvex (rounded on top and bottom) with a bevelled edge. The tablet has 'H' debossed (stamped into) one side and 'S14' on the other side. The tablets are presented in either aluminium foil on aluminium foil blister cards or plastic (HDPE) bottles. A bottle also contains a sachet of desiccant (drying material) and a polyester coil to keep the tablets in place. The bottle has a childproof plastic (polypropylene) screw cap with a pulp (cardboard-type material) liner.

The objective of the formulation development was to obtain a stable and robust formulation, bioequivalent to the WHO recommended comparator product Sovaldi® (sofosbuvir 400mg) tablets. The development strategy was based on information obtained from the manufacturer of the comparator product; same qualitative and quantitative composition and manufacturing process were used for the multisource product.

Based on the satisfactory data of optimization trials, the formulation was finalized resulting in a product matching the quality target product profile. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Specifications

The finished product specifications include appropriate tests for description, identification of the API (HPLC and UV), average weight, water content (KF), dissolution (UV detection), uniformity of dosage units (by weight variation), related substances (HPLC), assay (HPLC) and microbial limits. The test procedures have been adequately validated.

Stability testing

Stability studies have been performed 30°C/75%RH (zone IVb) as long-term storage condition and for six months at 40°C/75%RH as accelerated storage condition in the packaging proposed for marketing of the product. The product proved to be quite stable at these storage conditions. Based on the available stability data, the proposed shelf-life and storage conditions as stated in the SmPC are acceptable.

Conclusion

The quality part of the dossier is accepted.

3. Assessment of bioequivalence

The following bioequivalence study has been performed in 2015 according to internationally accepted guidelines.

A randomized, open-label, balanced, two-treatment, three-period, three-sequence, partial replicate, single oral-dose, crossover, reference scaled average bioequivalence study of Sofosbuvir 400 mg tablets of Hetero Labs Limited, India Comparing with that of Sovaldi™ (sofosbuvir) 400 mg tablets of Gilead Sciences, Inc. Foster City, CA 94404 in healthy, adult, human subjects under fed conditions. (study no. 039-15-WHO).

The objective of the study was to compare the bioavailability of the stated Sofosbuvir 400 mg tablet manufactured by/for Hetero Labs Limited, India (test drug) with the reference formulation Sovaldi™ (Gilead Sciences) and to assess bioequivalence. The comparison was performed as a single centre, open label, single dose, randomized, crossover study in healthy subjects under fed conditions. Each subject was assigned to receive each of the following two treatments in a randomized fashion, of which the reference twice:

Treatment T: Test – 1 tablet Sofosbuvir 400 mg

(sofosbuvir 400 mg)
Batch no. SOF115001.

Treatment R: Reference – 1 tablet Sovaldi™ 400 mg

(sofosbuvir 400 mg)

Batch no. NXVPD1.

A 10-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 24 samples within 48h post dose) were taken during each study period to obtain bioavailability characteristics AUC, C_{max} and t_{max} for bioequivalence evaluation. Drug concentrations for sofosbuvir were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 4 ng/ml for sofosbuvir.

The study was performed with 60 participants; data generated from a total of 54 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

Sofosbuvir

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)	1.75 ± 0.63	1.75 ± 0.71	-	-
C_{max} (ng/ml)	1116 ± 546 (997)	1164 ± 593 (1041)	95.7	87.2 – 105.2
AUC_{0-t} (ng.h/ml)	1486 ± 424 (1424)	1488 ± 495 (1413)	100.8	96.2 – 105.6
AUC_{0-inf} (ng.h/ml)	1492 ± 424 (1430)	1493 ± 495 (1419)	100.8	96.2 – 105.6

*geometric mean

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding sofosbuvir. Accordingly, the test Sofosbuvir 400 mg tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference Sovaldi™ (Gilead Sciences).

4. Summary of product safety and efficacy

[HP002 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, [HP002 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the WHO-recommended comparator product Sovaldi™ (sofosbuvir) 400 mg tablets of Gilead Sciences, Inc. Foster City, CA 94404 for which benefits have been proven in terms of clinical efficacy.

The clinical safety of [HP002 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 [HP002 trade name] is used in accordance with the SmPC.

Bioequivalence

The sofosbuvir 400 mg tablets of [HP002 trade name] have been shown to be bioequivalent with Sovaldi™ (sofosbuvir) 400 mg tablets (Gilead Sciences).

Efficacy and Safety

Regarding clinical efficacy and safety, [HP002 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 [HP002 trade name] was acceptable for the following indication: '**in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adults and in adolescents aged 12 to less than 18 years**', and would allow inclusion of [HP002 trade name], manufactured at Hetero Labs Limited, Unit-V, TSIIC Formulation SEZ, Survey No. 439,440,441 & 458 Polepally village, Jadcherla Mandal, Mahaboob Nagar (Dist) – 509301, Telangana, India, in the list of prequalified medicinal products.