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	[HP009 trade name][*]
Manufacturer of Prequalified Product	Strides Pharma Science Limited, KRS Gardens, Tablet Block, 36/7 Suragajakkanahalli Indlavadi Cross Anekal Taluk Bangalore, Karnataka 562 106 India
Active Pharmaceutical Ingredient(s) (API)	Sofosbuvir
Pharmaco-therapeutic group (ATC Code)	Direct acting antivirals (sofosbuvir: J05AX15)
Therapeutic indication	[HP009 trade name] tablets is indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adults and adolescents aged 12 to <18 years

1. Introduction

[HP009 trade name] is indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adults and adolescents aged 12 to <18 years.

[HP009 trade name] tablets should be initiated by a health care provider experienced in the management of hepatitis

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)

Sofosbuvir is a white to off-white non-hygroscopic powder, containing 5 stereogenic carbon centres and one chiral phosphor centre. The API is manufactured as a pure enantiomer: (S)-isopropyl 2-((S)-2-(((2R,3R,4R,5R)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl] methoxy)-(phenoxy) phosphorylamino] propanoate. Proof of the structure and absolute configuration has been established by single crystal X-ray crystallography.

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

Sofosbuvir exhibits polymorphism and it has been demonstrated by XRPD and DSC that the manufacturing process consistently yields one polymorphic form.

The API specifications include tests for description, identification (IR and HPLC), clarity of solution, loss on drying, related substances (HPLC), assay (HPLC), residual solvents, polymorphic identity (XRPD/DSC), elemental impurity-tin (ICP), specific optical rotation, foreign matter and particle size distribution. The test procedures have been adequately validated.

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, titanium dioxide, macrogol/polyethylene glycol, talc, FD& C Blue #1/ Brilliant blue FCF aluminium lake and FD& C Blue #2/ Indigo carmine FCF aluminium lake.

None of the excipients used in the manufacture of the tablets are of animal or human origin.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a blue coloured, capsule shaped, biconvex, bevel edged film-coated tablet, debossed with 400 on one side and plain on the other side.

The aim of the formulation development was to develop a stable and robust formulation that is bioequivalent to of the WHO recommended comparator product Sovaldi™ (sofosbuvir 400 mg tablets). The excipients were selected based on the excipients used in the comparator product and API-excipient compatibility studies. Sofosbuvir API is fluffy in nature and has poor flow; hence sofosbuvir along with the excipients were slugged and milled (via dry granulation) to obtain granular material with good flow and compressibility. 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 appearance, identification of the API (HPLC, UV), uniformity of weight, uniformity of dosage units (by weight variation), disintegration, water content (KF), dissolution (UV detection), assay (HPLC), related substances (HPLC) and microbial limits. The test procedures have been adequately validated

Stability testing

Stability studies have been performed at 30°C/75%RH (zone IVb) as long-term storage condition and for six months at 40°C/75%RH as accelerated 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.

Bioequivalence study of Sofosbuvir tablets 400 mg in normal, healthy, adult, human subjects under fed condition (study no. BE/15/114).

The objective of the study was to compare the bioavailability of the stated Sofosbuvir 400 mg tablet manufactured by/for Strides Shasun 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, randomized, three-period, partial reference replicate crossover study in healthy subjects under fed conditions. Each subject was assigned to receive each of the following two treatments in a randomized fashion (the reference was administered twice):

Treatment T: Test – 1 tablet sofosbuvir 400 mg
(sofosbuvir 400 mg)
Batch no. 7224246.

Treatment R: Reference – 1 tablet Sovaldi®
(sofosbuvir 400 mg)
Batch no. PKYBD.

A 7-day wash-out period was observed between administration of test and references. Serial blood samples (1 pre-dose sample and 21 samples within 12 h post dose) were taken during each study period to obtain bioavailability characteristics AUC, Cmax and tmax 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 14 ng/mL for sofosbuvir.

The study was performed with 60 participants; data generated from a total of 59 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 (geometric mean)	**Reference (R)** arithmetic mean ± SD (geometric mean)	**log-transformed parameters**	
			Ratio T/R (%)	**Conventional** 90% CI (ANOVAlog)
t_{max} (h)	2.0 (0.5 – 5.0)	1.75 (0.5 – 5.0)	–	–
C_{max} (ng/mL)	1242 ± 642 (1106)	1341 ± 810 (1129)	98.0	87.9 – 109.3
AUC_{0-t} (ng·h/mL)	1748 ± 526 (1663)	1711 ± 621 (1569)	106.0	101.0 – 111.3
AUC_{0-inf} (ng·h/mL)	1762 ± 510 (1704)	1779 ± 605 (1632)	104.5	99.8 – 109.4

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and Cmax 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

[HP009 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the reference product. According to the submitted data on quality and bioavailability [HP009 trade name] tablets is pharmaceutically and therapeutically equivalent and thus interchangeable with reference product Sovaldi® (Gilead Sciences International Ltd.) for which benefits have been proven in terms of clinical efficacy. The clinical safety of this product is considered

to be acceptable when guidance and restrictions as stated in the Summary of Product Characteristics are considered. Reference is made 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 [HP009 trade name] tablets is used in accordance with the SmPC.

Bioequivalence

[HP009 trade name] tablets have shown to be bioequivalent with reference product Sovaldi® (Gilead Sciences International Ltd.).

Efficacy and Safety

Regarding clinical efficacy and safety [HP009 trade name] tablets is considered effective and safe to use when the guidance and restrictions in the Summary of Product Characteristics 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 [HP009 trade name] tablets was acceptable for the following indication: "in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) in adults and adolescents aged 12 to <18 years" and has advised that the quality, efficacy and safety of [HP009 trade name] tablets are acceptable to allow inclusion of [HP009 trade name] tablets , manufactured at Strides Pharma Science Limited, KRS Gardens, 36/7 Suragajakkanahalli, Indlawadi Cross, Anekal Taluk, Bangalore, Karnataka, India in the list of prequalified medicinal products.