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	[HP003 trade name][*]
Manufacturer of Prequalified Product	European Egyptian Pharmaceutical Industries Alexandria-Cairo Desert Road Km 25 Amriya, Alexandria El Manshia Alex Egypt
Active Pharmaceutical Ingredient(s) (API)	Sofosbuvir
Pharmaco-therapeutic group (ATC Code)	Direct acting antivirals (sofosbuvir: J05AX15)
Therapeutic indication	[HP003 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.

1. Introduction

[HP003 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.

[HP003 trade name] 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. Evidence of the structure and absolute configuration has been confirmed by single crystal X-ray crystallography. Sofosbuvir exhibits polymorphism and it has been verified by XRPD and FT-IR that the manufacturing process consistently yields the same stable polymorphic form.

The API specifications include tests for appearance, solubility, identification (IR, HPLC and XRPD), water content, heavy metals, related substances (HPLC), assay (HPLC), residual solvents, density (bulk and tapped) and particle size distribution. The test procedures have been adequately validated.

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

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. Magnesium stearate is from plant origin. The commercially sourced proprietary film-coating mixture contains polyethylene glycol, polyvinyl alcohol, talc, titanium dioxide and iron oxide yellow. All the excipients used in the manufacture of the finished pharmaceutical product are well known pharmaceutical excipients with established uses in tablet formulations.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a pale yellow to yellow oblong biconvex, film-coated tablet.

The tablets are presented in a white 50ml HDPE bottle with aluminium seal and white child-resistant HDPE cap, containing 28 film-coated tablets and a desiccant. The bottle is packed in a carton box with a patient information leaflet.

The development of the formulation focused on patient safety, drug efficiency and bioequivalence to the WHO recommended comparator product (Sovaldi® 400 mg film-coated Tablets). The excipients selected are qualitatively same as those in the comparator product. API-excipient compatibility has been studied by DSC analysis. Sofosbuvir is cohesive and displays poor flowability. Dry granulation by slugging followed by direct compression was chosen as the manufacturing process to avoid potential degradation of sofosbuvir via hydrolysis during wet granulation and to mimic the comparator product. The formulation was optimised, targeting the dissolution profiles of the comparator product. Appropriate in-process controls were set to ensure batch-to-batch reproducibility.

Specifications

The finished product specifications include appropriate tests for appearance, average weight, uniformity of dosage units (weight variation and content uniformity), disintegration, water content (KF), dissolution (HPLC detection), identification (UV and HPLC), assay (HPLC), degradation products (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.

Randomized, four- way, four- period, fully replicated, single oral dose, open-label, crossover, bioequivalence study to compare sofosbuvir tablets (400 mg sofosbuvir) produced by European Egyptian Pharmaceutical Industries, versus Sovaldi® tablets (400 mg sofosbuvir) produced by Gilead Sciences, in healthy subjects under fed conditions (study no. BC-SOF-15/431).

The objective of the study was to compare the bioavailability of the stated sofosbuvir 400 mg tablet manufactured by/for European Egyptian Pharmaceutical Industries, Egypt (test drug) with the reference formulation Sovaldi® (Gilead Sciences, Inc.) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, four period, full replicate, crossover study in

healthy subjects under fed conditions. Each subject was assigned to receive each of the following two treatments twice in a randomized fashion:

Treatment T: Test – 1 tablet sofosbuvir 400 mg
(sofosbuvir 400 mg)
Batch no. 5105008.

Treatment R: Reference – 1 tablet Sovaldi®
(sofosbuvir 400 mg)
Batch no. 14SB010A.

A 7-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 20 samples within 10 h 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 analysed using a validated LC-MS/MS method. The limit of quantification was stated to be about 0.5 ng/mL for sofosbuvir.

The study was performed with 36 participants; data generated from a total of 33 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)	1.38 ± 0.87	1.51 ± 1.03	–	–
C_{max} (ng /mL)	941 ± 727 (731)	892 ± 611 (725)	99.8	87.4 – 114.0
AUC_{0-t} (ng·h/mL)	1257 ± 833 (1094)	1201 ± 725 (1057)	101.8	96.0 – 107.8
AUC_{0-inf} (ng·h/mL)	1260 ± 833 (1096)	1203 ± 725 (1060)	101.8	96.0 – 107.7

Conclusion
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, Inc.).

4. Summary of product safety and efficacy

[HP003 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, [HP003 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Sovaldi® (Gilead Sciences, Inc) for which benefits have been proven in terms of clinical efficacy.

The clinical safety of [HP003 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 [HP003 trade name] is used in accordance with the SmPC.

Bioequivalence

[HP003 trade name] has been shown to be bioequivalent with Sovaldi® (Gilead Sciences, Inc.)

Efficacy and Safety

Regarding clinical efficacy and safety, [HP003 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 [HP003 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 adolescents aged 12 to <18 years', and would allow inclusion of [HP003 trade name], manufactured at European Egyptian Pharmaceutical Industries, Alexandria-Cairo Desert Road Km 25, Amriya, Alexandria, El Manshia Alex, Egypt in the list of prequalified medicinal products.