# SCIENTIFIC DISCUSSION

**This part reflects the scientific knowledge and the information about this product available at the time of prequalification. Thereafter, updates may have become necessary which are included in parts 1 to 5 and, if related to pharmaceutical issues, also documented in part 8 of this WHOPAR.**

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| **Name of the Finished Pharmaceutical Product:** | [HP001 trade name][*] |
| **Manufacturer of Prequalified Product:** | Mylan Laboratories Limited (FDF Unit-1)<br>F-4 & F-12, MIDC, Malegaon<br>Sinnar, Nashik- 422 113<br>Maharashtra<br>India |
| **Active Pharmaceutical Ingredient (API):** | Sofosbuvir |
| **Pharmaco-therapeutic group (ATC Code):** | Direct acting antivirals (sofosbuvir: J05AX15) |
| **Therapeutic indication:** | [HP001 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. |

[*] Trade names are not prequalified by WHO. This is the national medicines regulatory authority's (NMRA) responsibility. Throughout this WHOPAR the Proprietary Name is given as an example only.

## 1. Introduction

[HP001 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.

[HP001 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 used in the manufacturer of [HP001 trade name] has been prequalified by WHO according to WHO's *Procedure for assessing the acceptability, in principle, of active pharmaceutical ingredients for use in pharmaceutical products* (WHO Technical Report Series No. 953, 2009, Annex 4). This procedure provides an assurance that sofosbuvir, used in the manufacture of [HP001 trade name], is of good quality and manufactured in accordance with WHO good manufacturing practices (GMP). API prequalification consists of a comprehensive evaluation procedure that has two components: Assessment of the API master file (APIMF) to verify compliance with WHO norms and standards, and assessment of the sites of API manufacture to verify compliance with WHO GMP requirements.

The API is of BCS low solubility; hence particle size distribution and polymorphism are considered critical parameters. These two parameters form part of the FPP manufacturer's API specifications, with acceptance criteria set on the information of the API lot used in the FPP biobatch. The API supplier produces polymorphic form-VI.

### 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, titanium dioxide, macrogol, talc, iron oxide yellow, iron oxide red and ferrosoferric oxide/black iron oxide. There are no excipients of animal or human origin used in the manufacture of the tablets. BSE/TSE compliance declarations were provided for all excipients.

### Finished pharmaceutical product (FPP)

*Pharmaceutical development and manufacture*

The multisource product is a peach coloured, capsule shaped, biconvex, bevelled edge film-coated tablet debossed with "SF400" on one side of the tablet and "M" on the other side. The tablets are presented in an HDPE bottle containing a canister filled with silica gel desiccant.

The development strategy focused on obtaining a pharmaceutically acceptable and stable multisource tablet, bioequivalent to the WHO recommended comparator product (Sovaldi® tablets, containing 400 mg sofosbuvir). The comparator product was characterized to define a quality target product profile. The excipients selected are the same as those in the comparator product, and are included in the formulation at levels suitable for the recognized purposes. The selection of the excipients was supported by API-excipient compatibility studies.

The compressibility index and Hausner ratio data showed that the API has very poor flow characteristics. Furthermore, poor flow of the blend was observed hence direct compression was ruled out. A dry granulation process using roller compactor to improve the flow properties of the blend was selected because of its simplicity. The formulation and process parameters were 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 description, identification of the API (HPLC and UV) and colorants, dissolution (UV detection), uniformity of dosage units (by mass variation), assay (HPLC), related substances (HPLC), water content (KF) 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 condition in the packaging proposed for marketing of the product. The product proved to be quite stable in these storage conditions, with very little degradation. 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.

Study title: Single dose oral bioequivalence study of Sofosbuvir film coated tablets 400 mg and 'Sovaldi™' (sofosbuvir) film coated tablets 400 mg in healthy adult human subjects under fed conditions (study no. BA15101179-01).

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

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| Treatment T: | Test – 1 tablet sofosbuvir 400 mg (sofosbuvir 400 mg) Batch no. 2008668 |
| 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 reference. Serial blood samples (1 pre-dose sample and 21 samples within 12 hours 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 10 ng/mL for sofosbuvir.

The study was performed with 80 participants; data generated from a total of 78 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) | 1.53 ± 0.67 | 1.57 ± 0.78 | - | - |
| $C_{max}$ (ng/ml) | 1287 ± 572 (1173) | 1286 ± 675 (1137) | 103.2 | 95.0 – 112.2 |
| $AUC_{0-t}$ (ng.h/ml) | 1503 ± 415 (1446) | 1525 ± 514 (1448) | 99.9 | 96.0 – 103.9 |
| $AUC_{0-inf}$ (ng.h/ml) | 1518 ± 416 (1462) | 1547 ± 515 (1473) | 99.2 | 95.4 – 103.2 |

* geometric mean

Conclusion

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 Science Inc.).

## 4. Summary of Product Safety and Efficacy

[HP001 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 [HP001 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with reference product Sovaldi® (Gilead Science Inc.) 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 [HP001 trade name] is used in accordance with the SmPC.

### Bioequivalence

[HP001 trade name] has shown to be bioequivalent with reference product Sovaldi® (Gilead Science Inc.).

### Efficacy and Safety

Regarding clinical efficacy and safety, [HP001 trade name] 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 [HP001 trade name] was acceptable for the following indication: **"in combinIndia, in 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 [HP001 trade name] are acceptable to allow inclusion of [HP001 trade name], manufactured at Mylan Laboratories Limited (FDF Unit-1), F-4 & F-12, MIDC, Malegaon, Sinnar, Nashik – 422113, Maharashtra, India, in the list of prequalified medicinal products.