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	[HP025 trade name][*]
Manufacturer of Prequalified Product	Mylan Laboratories Limited F- 4 & F-12, MIDC, Malegaon Sinnar, Nashik – 422 113 Maharashtra India
Active Pharmaceutical Ingredient(s) (API)	Daclatasvir (as dihydrochloride) and Sofosbuvir
Pharmaco-therapeutic group (ATC Code)	Direct acting antivirals (daclatasvir: J05AP07; sofosbuvir: J05AP08)
Therapeutic indication	[HP025 trade name] is indicated for the treatment of chronic hepatitis C virus (HCV) infection in adults.

1. Introduction

[HP025 trade name] is indicated for the treatment of chronic hepatitis C virus (HCV) infection in adults.

Treatment with [HP025 trade name] should be started and monitored by a health care provider experienced in the management of patients with hepatitis C.

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)

Daclatasvir dihydrochloride and sofosbuvir used in the manufacture of [HP025 trade name] have 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 the APIs, used in the manufacture of [HP025 trade name], are 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.

[*] 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 anhydrous lactose, 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, iron oxide yellow, iron oxide red and iron oxide black. BSE/TSE compliance declarations were provided for all the excipients

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a peach coloured, modified capsule shaped, biconvex beveled edge film coated tablet debossed with 'M' on one side and 'DTS' on the other side.

The tablets are presented in a round blue opaque HDPE bottle with either a blue opaque polypropylene screw or child resistant cap.

The development strategy focused on obtaining a pharmaceutically acceptable and stable multisource tablet, bioequivalent to the WHO recommended comparator products (Daklinza® tablets, containing 60 mg daclatasvir and Solvadi® tablets, containing 400mg sofosbuvir). Each comparator product was characterized to define a quality target product profile. The excipients selected were based on the available comparator products' information, API-excipient compatibility studies and prior experience of manufacturing similar types of immediate release solid oral dosage forms.

Based on the literature available on the comparator products and the poor flow properties of the APIs, a dry granulation process using the roll compaction technique was selected for the manufacturing of the product. The formulation and process parameters were optimised, targeting the dissolution profiles of the comparator products. 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 HPLC with PDA detector) and colorants, dissolution (HPLC detection), uniformity of dosage units (by content uniformity), 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 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 2018 according to internationally accepted guidelines:

A randomized, balanced, two-treatment, four-period, two-sequence, single-dose, full replicate, crossover oral bioequivalence study of My Hep DVIRTM (daclatasvir/sofosbuvir) 60 mg/400mg comprimes pellicules (tablets) of Mylan Laboratories Limited, India with Daklinza™ (daclatasvir) tablets 60 mg (Bristol-Myers Squibb Company, Princeton, NJ 08543, USA) and Sovaldi® (sofosbuvir) 400 mg film-coated tablets (Gilead sciences International Ltd. Cambridge CB 216GT United Kingdom), in normal healthy adult human subjects under fasting conditions (study no. C17437).

The objective of the study was to compare the bioavailability of the stated Daclatasvir/Sofosbuvir 60mg/400mg FDC tablet manufactured by/for Mylan Laboratories Limited, India (test drug) with the reference formulations Daklinza™ (Bristol-Myers Squibb Company) and Sovaldi® (Gilead Sciences International Ltd.) and to assess bioequivalence. The comparison was performed as a single centre, open label, randomized, full-replicate crossover study in healthy subjects under fasting conditions. Each subject was assigned to receive each of the following two treatments twice in a randomized fashion:

Treatment T: Test – 1 tablet Daclatasvir/Sofosbuvir 60mg/400mg (daclatasvir 60 mg + sofosbuvir 400 mg) Batch no. 3062517.

Treatment R: References
– 1 tablet Daklinza™ (daclatasvir 60 mg) Batch no. JJ0360.
– 1 tablet Sovaldi® (sofosbuvir 400 mg) Batch no. WPZPD.

A 15 day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 28 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 daclatasvir and sofosbuvir were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 10 ng/mL for daclatasvir as well as for sofosbuvir.

The study was performed with 48 participants; data generated from a total of 48 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

Daclatasvir

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)	1.65 ± 0.79	1.63 ± 0.89	–	–
C_{max} (ng/mL)	1545 ± 421 (1476)	1581 ± 436 (1506)	98.1	91.9 – 104.7
AUC_{0-t} (ng·h/mL)	16967 ± 5427 (15979)	16916 ± 4958 (16085)	99.3	94.0 – 105.0
AUC_{0-inf} (ng·h/mL)	18258 ± 5889 (17173)	18332 ± 5751 (17331)	99.1	93.7 – 104.8

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)	1.00 ± 0.70	1.19 ± 0.82	–	–
C_{max} (ng/mL)	1816 ± 848 (1625)	1583 ± 613 (1459)	111.4	100.6 – 123.4
AUC_{0-t} (ng·h/mL)	2034 ± 829 (1848)	1842 ± 641 (1741)	106.1	99.5 – 113.2
AUC_{0-inf} (ng·h/mL)	2045 ± 829 (1860)	1853 ± 641 (1753)	106.1	99.6 – 113.1

The results of the study show that preset acceptance limits of 80 -125 % are met by both AUC and C_{max} values regarding daclatasvir and sofosbuvir. Accordingly, the test Daclatasvir/Sofosbuvir 60mg/400mg FDC tablet meets the criteria for bioequivalence with regard to the rate and extent of absorption and is therefore bioequivalent to the reference formulations Daklinza™ (Bristol-Myers Squibb Company) and Sovaldi® (Gilead Sciences International Ltd.).

4. Summary of product safety and efficacy

[HP025 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, [HP025 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Daklinza™ (Bristol-Myers Squibb Company) and Sovaldi® (Gilead Sciences International Ltd.) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HP025 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 [HP025 trade name] is used in accordance with the SmPC.

Bioequivalence

[HP025 trade name] has been shown to be bioequivalent with Daklinza™ (Bristol-Myers Squibb Company) and Sovaldi® (Gilead Sciences International Ltd.).

Efficacy and Safety

Regarding clinical efficacy and safety, [HP025 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 [HP025 trade name] was acceptable for the following indication: **"for the treatment of chronic hepatitis C virus (HCV) infection in adults"**, and would allow inclusion of [HP025 trade name], manufactured at Mylan Laboratories Limited, F4 & F12, MIDC, Malegaon, Sinnar, Nashik – 422 113, Maharashtra, India in the list of prequalified medicinal products.