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	[HP016 trade name][*]
Manufacturer of Prequalified Product	Mylan Laboratories Limited (FDF Unit – 1) F-4 & F-12, MIDC, Malegaon Sinnar, Nashik – 422 113 Maharashtra India
Active Pharmaceutical Ingredient(s) (API)	Daclatasvir (as dihydrochloride)
Pharmaco-therapeutic group (ATC Code)	Antivirals for treatment of hepatitis C virus (HCV) infections. (ATC Code: J05AP07)
Therapeutic indication	[HP016 trade name] is indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) infection in adults.

1. Introduction

[HP016 trade name] is indicated in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) infection in adults.

[HP016 trade name] should be initiated by a health care provider experienced in the management of CHC infection.

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 used in the manufacture of [HP016 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 daclatasvir dihydrochloride, used in the manufacture of [HP016 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

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

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-N2.

Other ingredients

Other ingredients used in the core tablet formulation include anhydrous lactose, silicified microcrystalline cellulose, croscarmellose sodium, magnesium stearate and colloidal anhydrous silica, all being pharmacopoeia controlled. The commercially sourced proprietary film-coating mixture contains hypromellose, titanium dioxide, macrogol, iron oxide yellow and FD& C blue #2/indigo carmine aluminium lake. Magnesium stearate is from plant origin. BSE/TSE compliance declarations were provided for all the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a green, film-coated, capsule-shaped, biconvex, beveled edge tablet, debossed with 'D' on the left side and 'T' on the right side of the score line on one side and '6' on the left side and '0' on the right side of the score line on the other side. The score lines are intended for subdivision of tablets when half a tablet dose is to be administered as supported by divisibility studies during product development. The tablets are presented in a round, blue, opaque high density polyethylene (HDPE) bottle with a blue opaque polypropylene screw or child-resistant closure with wad containing aluminium induction sealing liner.

Two tablet strengths proportionally similar in composition were developed: 60 mg and 30 mg. The development focused on the higher strength which was used in the bioequivalence study

The development strategy focused on obtaining a pharmaceutically acceptable and stable multisource tablet, bioequivalent to the WHO recommended comparator product (Daklinza® tablets, containing 60 mg daclatasvir). The comparator product was characterized to define a quality target product profile. The excipients selected were based on the comparator product details and API-excipient compatibility studies.

Based on the EMA assessment report and literature available on the comparator product, a dry granulation process using the roll compaction technique to improve drug release profile and tablet properties was selected for the manufacture of the product. 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 (HPLC detection); uniformity of dosage units (by content uniformity); uniformity of mass; 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, 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 2017 according to internationally accepted guidelines.

A randomized, open-label, balanced, two-treatment, two-period, two-sequence, single-dose, crossover oral bioequivalence study of Daclatasvir tablets 60 mg of Mylan Laboratories Limited, India with Daklinza® (daclatasvir) tablets 60 mg of Bristol-Myers Squibb company, Princeton, NJ 08543, USA in normal healthy adult human subjects under fasting conditions (study no. C16264).

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

Treatment T:	Test – 1 tablet Daclatasvir 60 mg (daclatasvir 60 mg) Batch no. 2013431.
Treatment R:	Reference – 1 tablet Daklinza® (daclatasvir 60 mg) Batch no. 6B83225B.

An 8-day wash-out period was observed between administration of the test and reference. Serial blood samples (1 pre-dose sample and 22 samples within 72 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 daclatasvir were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 5 ng/mL for daclatasvir.

The study was performed with 40 participants. Data generated from a total of 38 subjects were utilized for analysis to establish pharmacokinetic parameters and assess bioequivalence.

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

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)	1.28 ± 0.54	1.31 ± 0.48	_	_
C_{max} (µg/mL)	2003 ± 492 (1936)	2064 ± 549 (1971)	98.2	91.1 – 105.9
AUC_{0-t} (µg·h/mL)	21 350 ± 6113 (20504)	21 846 ± 6302 (20914)	98.0	91.7 – 104.8
AUC_{0-inf} (µg·h/mL)	21 786 ± 6287 (20 917)	22 250 ± 6395 (21 305)	98.2	92.2 – 104.6

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

A biowaiver was granted for the additional 30 mg tablet strength (Mylan Laboratories Limited, India) in accordance to WHO guidelines. In comparison with the strength of the test product used in the bioequivalence study, the Daclatasvir 30 mg tablet was determined to be qualitatively essentially the same; the ratio of active ingredient and excipients between the strengths was considered essentially the same; and the dissolution profiles between the formulations for the APIs were determined the same.

4. Summary of product safety and efficacy

[HP016 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, [HP016 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the comparator product Daklinza® 60 mg Tablets (Bristol-Myers Squibb Company) for which benefits have been proven in terms of clinical efficacy. The clinical safety of [HP016 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 [HP016 trade name] is used in accordance with the SmPC.

Bioequivalence

[HP016 trade name] has been shown to be bioequivalent with Daklinza® 60 mg Tablets (Bristol-Myers Squibb Company, USA).

Efficacy and Safety

Regarding clinical efficacy and safety, [HP016 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 [HP016 trade name] was acceptable for the following indication: 'in combination with other medicinal products for the treatment of chronic hepatitis C (CHC) infection in adults', and would allow inclusion of [HP016 trade name], manufactured at Mylan Laboratories Limited (FDF Unit – 1), F- 4 & F-12, MIDC, Malegaon, Sinnar, Nashik – 422 113, Maharashtra, India in the list of prequalified medicinal products.