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:	[HP011 trade name][*]
Manufacturer of Prequalified Product:	Hetero Labs Ltd (Unit 5) Survey No. 439, 440, 441 & 458 TSIIC formulation SEZ Polepally village Jadcherla Mandal, Mahaboob Nagar District Telangana, 509 301 India
Active Pharmaceutical Ingredients (APIs):	Daclatasvir (as dihydrochloride)
Pharmaco-therapeutic group (ATC Code):	Antivirals for treatment of hepatitis C virus (HCV) infections. (ATC Code: J05AP07)
Therapeutic indication:	[HP011 trade name] is indicated in combination with other medicinal products for the treatment of chronic hepatitis C virus (HCV) infection in adults.

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

1. Introduction

[HP011 trade name] is indicated in combination with other medicinal products for the treatment of chronic hepatitis C virus (HCV) infection in adults.

[HP011 trade name] should be initiated by a health care provider experienced in the management of chronic HCV 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)

The APIMF of daclatasvir dihydrochloride, methyl[(2S)-1-{(2S}-2-[4-(4'-{2-[(2S)-1-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-2-pyrrolidinyl]-1H-imidazol-4-yl}-4-biphenylyl)-lH-imidazol 2-yl]-1-pyrrolidinyl}-3-methyl-1-oxo-2-butanyl]carbamate dihydrochloride has been accepted through WHO's APIMF procedure. The manufacture of daclatasvir dihydrochloride, which contains four chiral centres, entails several steps. The molecular structure and absolute stereochemistry were confirmed using techniques such as IR, UV, NMR and mass spectrometry, elemental analysis and chiral chromatography. Daclatasvir dihydrochloride exhibits polymorphism which is confirmed by XRPD.

The API specifications include tests for description, solubility, identification (IR, HPLC and XRPD), water content (KF), residue on ignition, hydrochloride content, related substances (HPLC), enantiomeric purity (HPLC), assay (HPLC), residual solvents (GC) and particle size distribution. Stability testing was conducted according to the requirements of WHO. The proposed re-test period is justified based on the stability results when the API is stored in the original packing material.

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, microcrystalline cellulose, croscarmellose sodium, colloidal silicon dioxide and magnesium stearate, all being pharmacopoeia controlled. The commercially sourced proprietary film-coating mixture contains hypromellose, titanium dioxide, macrogol and iron oxide yellow. BSE/TSE compliance declarations were provided for all the excipients.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a yellow, round, bevel-edged, biconvex, film-coated tablet, debossed with 'D14' on one side and 'H' on the other side. The tablets are presented in either white, opaque HDPE containers and closed with white, opaque polypropylene child-resistant plastic caps with pulp liners or in clear PVC/Aclar-Alu blisters.

Two tablet strengths, proportionally similar in composition of the core tablets and manufactured according to the same procedure, were developed; 60mg and 30mg. The development focused on the higher strength which was used in the bioequivalence study.

The objective of the development work was to develop a stable formulation, bioequivalent to the WHO recommended comparator product (Daklinza® tablets, containing 60 mg daclatasvir). Following an analysis of the comparator product, a quality target product profile was defined for the multisource product. The excipients selected were based on comparator product composition, pre-formulation studies and API-excipient compatibility studies. Dry granulation process was selected to improve the flow properties of the API. 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), average weight, water content (KF), dissolution (HPLC detection), uniformity of dosage units (by content uniformity), related substances (HPLC), assay (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 packages 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. The tablets must be protected from light and moisture.

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.

An open label, balanced, randomized, two-treatment, two-period, two-sequence, single oral dose, crossover, bioequivalence study of Daclatasvir Tablets 60 mg of Hetero Labs Limited, India comparing with that of 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. 746-15).

The objective of the study was to compare the bioavailability of the stated Daclatasvir 60 mg tablet manufactured by/for Hetero Labs Limited, India (test drug) with the reference formulation Daklinza® (Bristol-Myers Squibb) 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. DAC16008.
Treatment R:	Reference – 1 tablet Daklinza® (daclatasvir 60 mg) Batch no. AAK1913.

An 8-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 23 samples within 72 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 daclatasvir were analyzed using a validated LC-MS/MS method. The limit of quantification was stated to be about 10 ng/mL for daclatasvir.

The study was performed with 42 participants. Data generated from a total of 39 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 (*)	Reference (R) arithmetic mean ± SD (*)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)[#]	1.25 (0.75 – 2.5)	1.25 (0.75 – 2.75)	-	-
C_{max} (ng/mL)	1526 ± 407 (1471)	1566 ± 441 (1509)	97.5	89.9 – 105.8
AUC_{0-t} (ng.h/mL)	17283 ± 6288 (16235)	18009 ± 7888 (16877)	96.2	88.6 – 104.5
AUC_{0-inf} (ng.h/mL)	17771 ± 6411 (16713)	18555 ± 8310 (17362)	96.3	88.8 – 104.4

*geometric mean; [#]median (range)

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).

A biowaiver was granted for the additional 30 mg tablet strength (Hetero Labs Limited, India) in accordance to the WHO guideline. 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 API were determined to be the same.

4. Summary of Product Safety and Efficacy

[HP011 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the comparator product. [HP011 trade name] fulfilled all criteria for waiving an in-vivo bioequivalence study as per relevant WHO guidance.

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 [HP011 trade name] is used in accordance with the SmPC.

Bioequivalence

[HP011 trade name] fulfilled all criteria for waiving an *in vivo* bioequivalence study as per relevant WHO guidance. Hence, [HP011 trade name] and Daklinza® 30 mg Tablets (Bristol-Myers Squibb Company) can be considered bioequivalent.

Efficacy and Safety

Regarding clinical efficacy and safety, [HP011 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 the WHO's assessment of data on quality, bioequivalence, safety and efficacy the team of assessors considered that the benefit–risk profile of [HP011 trade name] was acceptable for the following indication: '**in combination with other medicinal products for the treatment of**

chronic hepatitis C virus (HCV) infection in adults' and has advised that the quality, efficacy and safety of [HP011 trade name] allow inclusion of [HP011 trade name], manufactured at Hetero Labs Ltd (Unit 5), Survey No. 439, 440, 441 & 458, TSIIC formulation SEZ, Polepally village, Jadcherla Mandal, Mahaboob Nagar District, Telangana, 509 301, India in the list of prequalified medicinal products.