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	[HP022 trade name][*]
Manufacturer of Prequalified Product	Cipla Limited, Plot A-42 (Unit 2), MIDC, Patalganga, Raigad District, Maharashtra 410 220, India
Active Pharmaceutical Ingredient(s) (API)	Daclatasvir (as dihydrochloride)
Pharmaco-therapeutic group (ATC Code)	Antivirals for treatment of hepatitis C virus (HCV) infections. (J05AP07)
Therapeutic indication	[HP022 trade name] is indicated in combination with other medicinal products for the treatment of chronic hepatitis C virus (HCV) infection in adults.

1. Introduction

[HP022 trade name] is indicated in combination with other medicinal products for the treatment of chronic hepatitis C virus (HCV) infection in adults.

[HP022 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)

Daclatasvir dihydrochloride 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 [HP022 trade name], is of good quality and manufactured in accordance with WHO Good Manufacturing Practices. 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 hypromellose, titanium dioxide, macrogol/polyethylene glycol, iron oxide yellow and FD& C Blue #2/Indigo carmine aluminium lake. None of the excipients used in the manufacture of the tablets are of animal or human origin.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is a light green coloured, circular, biconvex film-coated tablet debossed with 'C60' on one side and plain 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 heat seal liners or in plain PVC/PE/PVDC-Alu blisters.

Two tablet strengths, proportionally similar in composition of the core tablets and manufactured according to the same procedure, were developed; 60 mg and 30 mg. 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). The quality target product profile was defined for the multisource product based on published literature, characterization of the comparator product and consideration of the comparator product label. The excipients were selected based on the qualitative composition of the comparator product and API-excipient compatibility studies. As per the literature of the comparator product, dry granulation process was selected for the multisource 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, UV) and colorants, average weight, water content (KF), uniformity of dosage units (by content uniformity), dissolution (HPLC detection), 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.

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.

Study title:

An open label, balanced, randomized, two-treatment, four-period, two-sequence, single oral dose, full replicate crossover bioequivalence study of Daclatasvir Tablets 60 mg of Cipla Limited, India and

DaklinzaTM (daclatasvir) Tablets 60 mg of Bristol-Myers Squibb Pharma EEIG, UK in normal, healthy, adult human subjects under fasting condition (study no. 0660-17).

The objective of the study was to compare the bioavailability of the stated daclatasvir 60 mg tablet manufactured by/for Cipla 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, fully 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 60 mg
(daclatasvir 60 mg)
Batch no. PB80053.

Treatment R: Reference – 1 tablet Daklinza™
(daclatasvir 60 mg)
Batch no. AAR7386.

A 7-day wash-out period was observed between administration of tests and/or references. Serial blood samples (1 pre-dose sample and 20 samples within 48 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 10 ng/mL for daclatasvir.

The study was performed with 44 participants; data generated from a total of 42 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)	1.33 (0.75 – 4.0)	1.33 (0.75 – 5.0)	–	–
C_{max} (ng/mL)	1703 ± 467 (1616)	1629 ± 522 (1534)	105.3	98.5 – 112.7
AUC_{0-t} (ng·h/mL)	18933 ± 5815 (17752)	17791 ± 5779 (16904)	105.0	99.3 – 111.0
AUC_{0-inf} (ng·h/mL)	20190 ± 6575	18865 ± 6476		

The results of the study show that preset acceptance limits of 80 – 125 % are met by both AUC and Cmax 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).

4. Summary of product safety and efficacy

[HP022 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, [HP022 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 this product is considered to be acceptable when guidance and restrictions as stated in the Summary of Product Characteristics are taken into account. 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 [HP022 trade name] is used in accordance with the SmPC

Bioequivalence

[HP022 trade name] has shown to be bioequivalent with Daklinza® 60 mg Tablets (Bristol-Myers Squibb Company, USA).

Efficacy and Safety

Regarding clinical efficacy and safety, [HP022 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 [HP022 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 [HP022 trade name] allow inclusion of [HP022 trade name], manufactured at Cipla Limited, Plot A-42 (Unit 2), MIDC, Patalganga, Raigad District, Maharashtra 410 220, India in the list of prequalified medicinal products.