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	[HP034 trade name][*]
Manufacturer of Prequalified Product	Zydus Lifesciences Limited Kundaim Industrial Estate, Plot No.203-213, Kundaim, Goa-403 115, 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	[HP034 trade name] is indicated in combination with other medicinal products for the treatment of hepatitis C infection in adults and children.

1. Introduction

[HP034 trade name] is indicated in combination with sofosbuvir for the treatment of chronic hepatitis C virus (HCV) infection in adults and children.

[HP034 trade name] should be initiated by a health care provider experienced in the management of chronic hepatitis C virus.

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 [HP034 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 lactose monohydrate, 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 and FD&C yellow # 6/sunset yellow FCF aluminium lake. TSE/BSE compliance declarations were provided for all the excipients. Lactose monohydrate and magnesium stearate are of bovine and vegetable origin respectively.

Finished pharmaceutical product (FPP)

Pharmaceutical development and manufacture

The multisource product is an orange, round, film coated tablet. It is biconvex (rounded on top and bottom) with a flat edge. The tablet has '60' debossed (stamped into) one side and 'D' on the other side. The tablets are presented in either aluminium foil on aluminium foil blister cards or plastic (HDPE) bottles. The bottle has an aluminium/plastic foil seal and a white, childproof plastic (polypropylene) continuous threaded cap.

Two tablet strengths, proportionally similar in composition 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 obtain a safe and efficacious formulation, bioequivalent to the WHO recommended comparator product (Daklinza® tablets, containing 60 mg daclatasvir). The quality target product profile was defined based on the physico-chemical characteristics of the comparator product as well as the in-vitro dissolution profile. The excipients were selected based on their similarity to the comparator product and API-excipient compatibility studies. On the basis of developmental trials and the data obtained, it was concluded that the direct compression manufacturing process was best suited for further development of 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.

According to a risk evaluation by the applicant, the FPP appears to have no potential to contain nitrosamine impurities and hence no risk was identified.

Specifications

The finished product specifications include appropriate tests for description, identification of the API (HPLC, UV), uniformity of dosage units (by content uniformity), average weight, dissolution (UV detection), assay (HPLC), related substances (HPLC), water content (KF), hardness 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 storage condition in the package 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.

Single dose oral bioequivalence study of Daclatasvir tablets 60 mg and 'DAKLINZA™' (daclatasvir) tablets 60 mg in healthy adult human subjects under fasting conditions (study no. BA18086187).

The objective of the study was to compare the bioavailability of the stated Daclatasvir 60 mg tablet manufactured by/for Cadila Healthcare 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, single dose, 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. GE60098.
Treatment R:	Reference – 1 tablet Daklinza™ 60 mg (daclatasvir 60 mg) Batch no. 6B82819B.

A 7-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 26 samples within 72h 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 26 participants; data generated from a total of 24 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)	1.40 ± 0.53	1.47 ± 0.73	-	-
C_{max} (ng/mL)	1436 ± 477 (1326)	1449 ± 390 (1404)	94.4	80.8 – 110.2
AUC_{0-t} (ng·h/mL)	14678 ± 4523 (13740)	15109 ± 4903 (14446)	95.1	83.5 – 108.4
AUC_{0-inf} (ng·h/mL)	14858 ± 4558 --	15341 ± 4977 --	-	-

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).

4. Summary of product safety and efficacy

[HP034 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, [HP034 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 [HP034 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 [HP034 trade name] is used in accordance with the SmPC.

Bioequivalence

[HP034 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, [HP034 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 [HP034 trade name] was acceptable for the following indication: ' treatment of hepatitis C infections in adults and children indication', and would allow inclusion of [HP034 trade name], manufactured at Zydus Lifesciences Limited, Goa-403 115, India in the list of prequalified medicinal products.