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	[HP028 trade name][*]
Manufacturer of Prequalified Product	Laurus Labs Limited (Unit-II) Plot No. 19, 20 & 21 Western Sector, APSEZ, Gurajapalem Village Rambilli Mandal, Anakapalli - 531011, Andhra Pradesh, India
Active Pharmaceutical Ingredients (APIs)	Daclatasvir (as dihydrochloride)
Pharmaco-therapeutic group (ATC Code)	Antivirals for treatment of HCV infections (J05AP58)
Therapeutic indication	[HP028 trade name] is indicated in combination with other medicinal products for the treatment of chronic hepatitis C virus (HCV) infection in adults.

1. Introduction

[HP028 trade name] is indicated in combination with other medicinal products for the treatment of chronic hepatitis C virus (HCV) infection in adults.

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 [HP028 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 pharmacopoeia controlled. The commercially sourced proprietary film-coating mixture contains polyvinyl alcohol- partially hydrolysed, titanium dioxide, macrogol/polyethylene glycol and talc. The magnesium stearate is of 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 white to off-white, round, biconvex film-coated tablet, debossed with 'D' and '6' on either side of the break line on one side and plain on the other side. The break line is intended for subdivision of tablets when half a tablet dose is to be administered, as supported by divisibility studies. The tablets are presented in either a white, opaque 60cc /33mm HDPE bottle containing a 1-g silica gel canister closed with 33mm- 400 ARGUS polypropylene child-resistant closure with TEKNIPLEX HS 123 induction sealing wad or a white, opaque 250cc / 53mm HDPE bottle containing a 1g silica gel canister and closed with a cap (53mm- 400 screw polypropylene closure with TEKNIPLEX HS 123 induction sealing wad).

Two tablet strengths, proportionally similar in composition 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 using roller compactor 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 colorant, 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 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.

An open label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose, cross-over, oral bioequivalence study of Daclatasvir tablets 60 mg of Laurus Labs Limited, India comparing with that of Daklinza® (daclatasvir) 60 mg tablets of Bristol-Myers Squibb Pharma EEIG, United Kingdom in healthy, adult, human subjects under fasting conditions (study no. 607/18).

The objective of the study was to compare the bioavailability of the stated daclatasvir 60 mg tablet manufactured by/for Laurus Labs Limited, India (test drug) with the reference formulation Daklinza® (Bristol-Myers Squibb Pharma) 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. E1800211

Treatment R: Reference – 1 tablet Daklinza® 60 mg (daclatasvir 60 mg) Batch no. AAM5585

An 11-day wash-out period was observed between administration of test and reference. Serial blood samples (1 pre-dose sample and 25 samples within 60 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 48 participants. Data generated from a total of 47 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)	Reference (R) arithmetic mean ± SD (geometric)	log-transformed parameters	
			Ratio T/R (%)	Conventional 90% CI (ANOVAlog)
t_{max} (h)[#]	1.25 (0.67 – 3.5)	1.25 (0.67 – 4.5)	-	-
C_{max} (ng/mL)	1936 ± 541 (1868)	1756 ± 546 (1655)	112.8	103.6 – 122.9
AUC_{0-t} (ng.h/mL)	21150 ± 9103 (19808)	18669 ± 5831 (17612)	112.5	103.4 – 122.4
AUC_{0-inf} (ng.h/mL)	21821 ± 10295 (20289)	19066 ± 5983 (17992)	112.8	103.6 – 122.8

The results of the study show that the pre-set 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 regards to the rate and extent of absorption and is therefore bioequivalent to the reference Daklinza® 60 mg (Bristol-Myers Squibb Pharma).

A biowaiver was granted for the additional 30 mg tablet strength (Laurus Labs 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 essentially the same qualitatively, i.e., the ratio of active ingredient and excipients between the strengths and the dissolution profiles between the formulations for the APIs were determined to be essentially the same.

4. Summary of product safety and efficacy

[HP028 trade name] has been shown to conform to the same relevant standards of quality, efficacy and safety as those required of the innovator product. According to the submitted data on quality and bioavailability [HP028 trade name] is pharmaceutically and therapeutically equivalent and thus interchangeable with the innovator product Daklinza® (Bristol-Myers Squibb Pharma) 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 considered. 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 [HP028 trade name] is used in accordance with the SmPC.

Bioequivalence

[HP028 trade name] has shown to be bioequivalent with the innovator, Daklinza® (Bristol-Myers Squibb Pharma).

Efficacy and Safety

Regarding clinical efficacy and safety, [HP028 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 WHO's assessment of data on quality, safety and efficacy the team of assessors considered that the benefit risk profile of [HP028 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 product characteristics are acceptable to allow inclusion of [HP028 trade name], manufactured at Laurus Labs Limited (Unit 2), Plot No. 19, 20 & 21, Western Sector, APSEZ, Gurajapalem Village, Rambilli Mandal, Anakapalli - 531011, Andhra Pradesh, 531011, India, in the list of prequalified medicinal products.