THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR DACLAVIRDIN (60MG DACLATASVIR (AS DIHYDROCHLORIDE)) FILM COATED TABLETS

Version number 1
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1. Introduction

Daclavirdin is a generic medicine of Daklinza 60 mg (Daclatasvir 60mg) Film Coated tablets manufactured by Bristol-Myers Squibb Pharma. Daclavirdin is antihepatitis C medicine belong to direct-acting antiviral group. Daclavirdin contains Daclatasvir Dihydrochloride. Daclatasvir is an inhibitor of non-structural protein 5A (NS5A), a multifunctional protein that is an essential component of the HCV replication complex. Daclatasvir inhibits both viral RNA replication and virion assemble. Daclavirdin is approved in Tanzania for use only in adult patients.

1.1 Product details

Registration number	TAN 21 HM 0454
Brand name	Daclavirdin
Generic name, strength, and form	Each film-coated tablet contains Daclatasvir dihydrochloride 65.921 mg equivalent to Daclatasvir 60 mg
ATC classification	ATC Code- J05AP07, Direct-acting antiviral
Distribution category	POM
Country of origin	Egypt
Associated product	N/A
Marketing Authorization Holder	Eva Pharma for Pharmaceuticals and Medical Appliances 176 El Sadat at, Kafr EL Gabal, Haram, Giza Egypt. E-mail: Michael.nagy@evapharma.com
Local Technical Representative	Melody Pharma (T) Ltd Plot No. 35 Block No 57, Kariakoo Livingstone/Narung'ombe Street Tanzania.

1.2 Assessment procedure

The application for registration of Daclavirdin was submitted on 24 April 2018. The product underwent full assessment. Assessment was completed in 3 (three) rounds of evaluation and the product was registered on 26 November 2021.

1.3 Information for users

Visual description of the finished product	Pale green to green round biconvex film coated tablets plain from both sides
Primary packing material	Alu-Alu coated PVC film-blister
Secondary packing materials	A printed carton box
Shelf-life and storage condition	24 months, store in a dry place, at a

	temperature not exceeding 30^{o}C.
Route of administration	Oral
Therapeutic indications	Daclavirdin is indicated in combination with other medicinal products for the treatment of chronic hepatitis C virus (HCV) infection in adults

2. Labelling and product information

Summary of product characteristics
The SmPC included all the relevant information to ensure correct and safe use of the medicine by healthcare providers. The complete SmPC can be accessed here.

Package insert/leaflet
The package insert is confirmed to be derived from the SmPC and contains sufficient data for the end user. Since the product is POM, the package insert contains full prescribing information as per SmPC.

Container labels
The product label information is presented in English. Details in the secondary pack label include:
Brand name: Daclavirdin

Composition: Each film-coated tablet contains Daclatasvir dihydrochloride 65.921 mg equivalent to Daclatasvir 60 mg

Pack size: 28 film-coated tablets

Manufacturing details: batch number, manufacturing date, and expiry date

Storage conditions: Store in a dry place, at a temperature not exceeding 30^{o}C.

Manufacturer address: physical address of release site

Unique identifier: Not applicable

Special warnings/precautions or instructions for use: This product contains lactose.

The details of the primary pack include:

Brand name and strength: Daclavirdin

Manufacturing details: batch number, manufacturing date and expiry date

Name of manufacturer: Eva Pharma for Pharmaceuticals and Medical Appliances

The content of the primary and secondary labels was aligned to the requirements of the Part V of the Compendium: Guidelines on Format and Content of Product Labels for Medicinal products. The label contains sufficient information for proper identification of the medicine and post marketing follow up of the product.

Mock labels are appended as annex I.

3. Scientific discussion

Quality of Active Pharmaceutical Ingredients

Information on the quality of the API was submitted in form of DMF.

General Information

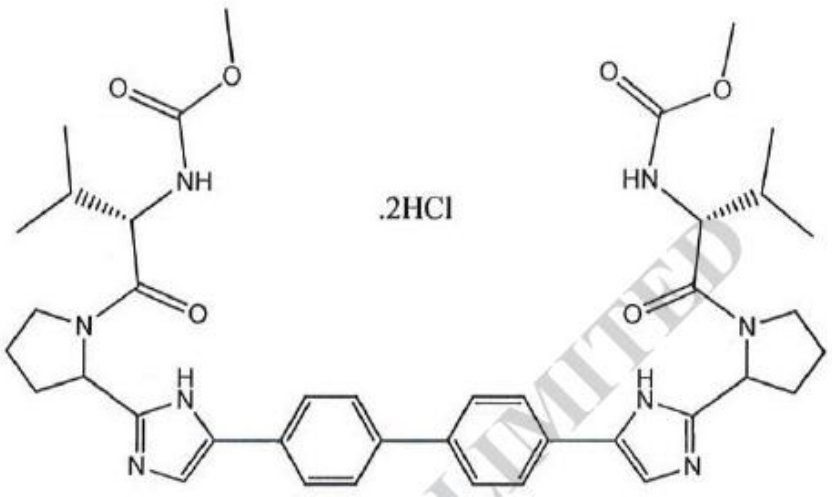
Daclatasvir dihydrochloride API is non-compendia.

Molecular formula: $C_{40}H_{52}Cl_2N_8O_6$

Chemical name:

Methyl ((1S)-1-(((2S)-2-(5-(4'-(2-((2S)-1-((2S)-2-((methoxycarbonyl) amino)-3 methylbutanoyl)-2-pyrrolidinyl)-1Himidazol-5-yl)-4-biphenylyl)-1H-imidazol-2-yl)-1 pyrrolidinyl) carbonyl)-2-methylpropyl) carbamate dihydrochloride
OR
Dimethyl((2S,2'R)-(2,2'-(5,5'-([1,1'- biphenyl]-4,4'-diyl) bis (1H-imidazole-5,2 -diyl))bis(pyrrolidine-2,1-diyl))bis (3-methyl-1-oxobutane-2, 1-diyl)) dicarbamate dihydrochloride

Structure:



General properties

Daclatasvir is a white to yellow crystalline non-hygroscopic powder. It is freely soluble in water, dimethyl sulfoxide, methanol; soluble in ethanol (95%); practically insoluble in dichloromethane, tetrahydrofuran, acetonitrile, acetone and ethyl acetate. The substance shows polymorphism and stereoisomerism. The manufacturer consistently produces the correct isomer and the same polymorphic form.

According to Biopharmaceutics Classification System (BCS), Daclatasvir is classified as Class 2 compound (low solubility, high permeability) hence particle size distribution (PSD) and polymorphism are considered critical parameters and form part of the API specifications.

Manufacture

Daclatasvir dihydrochloride API manufacturer is Optimus Drugs Private Limited, Survey No.239 & 240; Dothigudem Village, Pochampally Mandal, Yadadri (Dist) – 508 284.Telangana, India. The manufacturing complies with GMP requirements as evidenced by the GMP certificate issued by the Drugs Control Administration, Telangana. Daclatasvir dihydrochloride API is manufactured by chemical synthesis using conventional techniques. Sufficient controls of quality of materials and in-process checks were employed throughout the manufacturing process.

Specifications

The API specifications were set as per in-house standards and ICHQ3A. The parameters monitored during quality control are: Description, solubility, identity (IR and HPLC), specific rotation, residue on ignition, hydrochloric acid content, heavy metals, melting range, limit of enantiomer (HPLC), residual solvent (GC), assay (HPLC), related impurities (HPLC), water content (KF), particle size (laser diffraction), and polymorphism (XRPD). Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Daclatasvir dihydrochloride API is 18 months when packed in transparent polythene bag, this bag is kept in black PE bag and into triple laminated aluminum bag into HDPE container with storage condition ‘Store below 25°C’.

Quality of the Finished Pharmaceutical Product

Formulation

Daclavirdin is a pale green to green round biconvex film coated tablets plain from both sides.

Daclavirdin contains the Daclatasvir dihydrochloride and other ingredients listed here after: Lactose anhydrous, Microcrystalline cellulose, Croscarmellose sodium, Colloidal silicon dioxide, Magnesium stearate, Opadry green 02B210002 (Hypromellose, Titanium dioxide, Iron oxide yellow, FD & C Blue #2/Indigo Carmine Aluminium lake). The quantities of all ingredients are confirmed to be in line with the recommendations of Handbook of Pharmaceutical Excipients, 8th Edition in terms of function and quantities.

Manufacture

The finished product manufacturers are EVA Pharma for Pharmaceuticals and Medical Appliances,176 El-Sadat, Kafr El-Gabal, Pyramids, Giza, Egypt. The compliance of the sites to TMDA GMP standards was confirmed through desk-review on 17 June 2021

Specifications

The FPP is non-compendia. The manufacturer controls the quality of the finished product as per in-house standards and ICH requirements. The parameters monitored during quality control are: Description, uniformity of weight, disintegration, resistance to crushing, identification of API (UV and HPLC), identification of colourant, assay, dissolution, content uniformity, related impurities, and microbial purity. Compliance to the standard was established using batch analysis data and stability data.

Stability and container closure system

Stability studies were conducted on a 3(three) batches of the finished product stored at 30 ± 2°C & RH: 75 ± 5% RH for 24 months and 40± 2°C & RH: 75% ± 5% RH for 6 months. Based on the stability data presented, the approved shelf-life is 24 months when stored in Alu-Alu coated PVC film-blister with storage condition ‘Store in a dry place, at a temperature not exceeding 30°C’.

Safety and efficacy information

Safety and efficacy of Daclavirdin was established through a bioequivalence trial.

BE trial report number 175/2015 was submitted.

Study title	In vivo bioequivalence of Daclavirdin 60 mg Film Coated tablets, made by EVA Pharma for Biothecary and Daklinza 60 mg FC tablets, made by Bristol-Myers Squibb Pharma EEIG, Uxbridge Business Park, Sanderson Road, Uxbridge UB 1DH, United Kingdom
Study design	Single-dose, Fasting study, two-treatment, two-period, two-sequence (2 x 2) randomized crossover design with one week wash out period

Study site	Pharmagene Specialised Analytical Services, 5 Amman Street, Dokki, Giza 12311, Egypt	
Study dates	03/11/2015- 21/11/2015	
Primary objective	The study was designed to compare the rate, extent of absorption and safety of test Product Daclavirdin 60 mg (Daclatasvir 60mg) Film Coated tablets, manufactured by EVA Pharma with reference product: Daklinza 60 mg Film Coated tablets (Daclatasvir 60mg) of Bristol-Myers Squibb Pharma EEIG, Uxbridge Business Park, Sanderson Road, Uxbridge UB 1DH, United Kingdom in healthy, adult, human subjects under fasting conditions in a randomised, crossover design	
Secondary objective	To monitor the safety and tolerability of a single dose of Daclatasvir 60mg tablets when administered in 31 healthy adult human subjects under fasting condition	
Number of participants	Planned-31 subjects Enrolled-31 subjects Dosed-31 subjects Withdrawn - 00 subjects Bio-sample analyzed - 31 subjects Pharmacokinetic and statistical data analyzed – 31subjects	
Monitored parameters	Tmax, Cmax, AUC0→t, AUC0→∞, AUC% Extrapolation Kel and T1/2	
Investigational medicinal products	Test Product	Reference product
	Strength: 60 mg Batch number: 498105 Expiry date: 10/2017	Strength: 60 mg Batch number: 4G80897 Expiry date: 07/2016
Analytical method	Liquid chromatography electrospray mass spectrometry (LC-ESI-MS/MS) method was used for the determination of plasma concentrations of analyte	
Statistical method	SAS® procedure PROC GLM Software (SAS Institute Inc., USA)	

Efficacy results are summarized as follows:

Parameter	**Test**	**Reference**	**90 % Confidence interval**	**DF**	**CV (%)**
AUC0-t (hr.ng/mL)	18151.753	17786.169	96.10098-102.05544	29	Complete
AUC0-inf (ng.hr/mL)	18419.942	18121.332	95.79959-101.64784	29	Complete
Cmax (ng/mL)	1579.6206	1530.3361	96.78212-103.22049	29	Complete

The acceptance limits of 80 – 125% are met by the AUC and Cmax values. Furthermore, the safety profile of the test product is similar to that of reference product. Therefore, Daclavirdin 60 mg (Daclatasvir 60mg) Film Coated tablets, manufactured by EVA Pharma is equivalent and interchangeable with Daklinza 60 mg Film Coated tablets (Daclatasvir 60mg) of Bristol-Myers Squibb Pharma EEIG, United Kingdom under acceptable in vivo experimental conditions.

4. Benefit-Risk Assessment and Conclusion

On basis of the data submitted, the current state of knowledge and compliance to Good Manufacturing Practice, the benefit of the product outweighs the risks associated with its use when used in accordance to the summary of product characteristics. Daclavirdin is recommended for registration.

5. Post-approval updates

Variation applications

Reference number	Date submitted	Change requested	Recommendation	Granting date

Feedback from pharmacovigilance, post marketing surveillance and enforcement activities

Type of feedback	Impact	Response

Re-registration applications

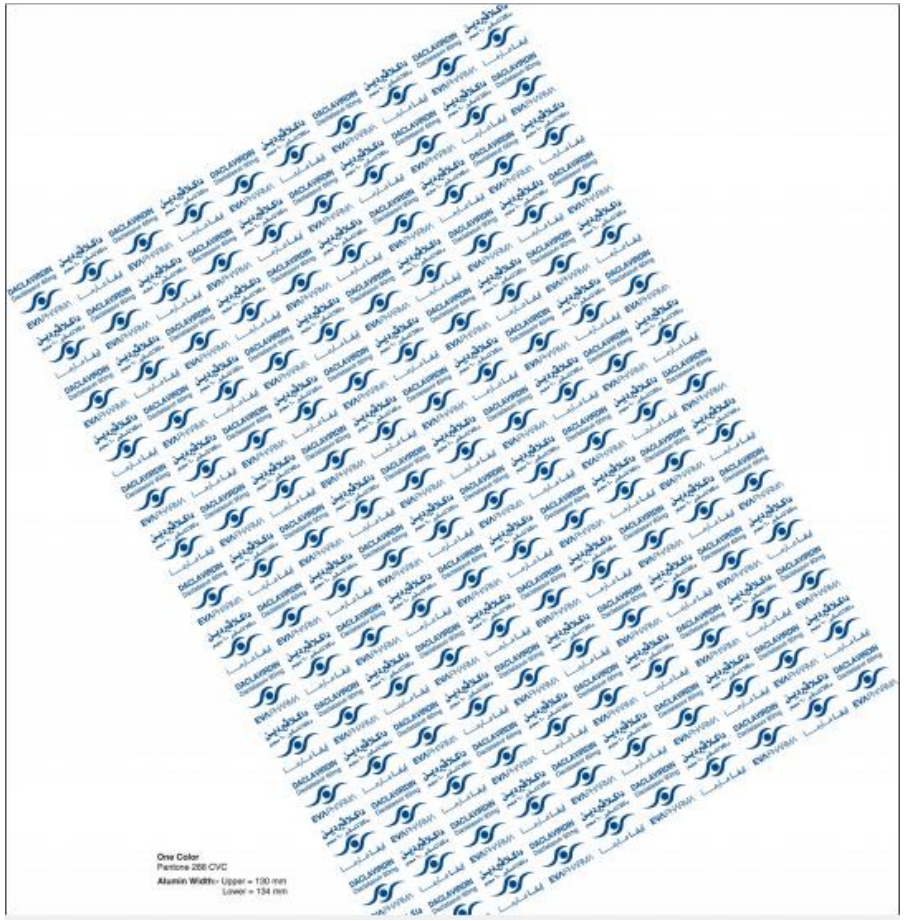
Application for renewal of registration was submitted on <DDMMYYYY>. The application was finalized in <number> rounds of evaluation. The product was confirmed to still be compliant to the standards of quality, safety and efficacy, hence registration was renewed on <DDMMYYYY>.

PART 5: CHANGE HISTORY

Version number	Date	Description of update	Section(s) Modified	Approval date

Annex I: Mock up labels;

Primary pack label;



Secondary pack label;

Effective date: 03/10/2022