THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR DARUNAVIR (400MG DARUNAVIR (AS ETHANOLATE)) FILM COATED TABLETS

Version number 1
05 January, 2022

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1. Introduction

Darunavir is a generic medicine of Prezista 400 mg, film-coated tablets of Janssen-Cilag International NV, is an antiretroviral medicinal product of protease inhibitor family which selectively inhibits the cleavage of HIV-1 encoded Gag-Pol polyproteins in infected cells, thereby preventing the formation of mature virus particles. Darunavir is approved in Tanzania for use in adult and pediatric patients 3 years of age and older or weighing ≥15 kg.

1.1 Product details

Registration number	TAN 21 HM 0455
Brand name	Darunavir
Generic name, strength, and form	Each film-coated tablet contains Darunavir ethanolate equivalent to Darunavir 400 mg
ATC classification	ATC Code- J05AE10 Antivirals for systemic use, protease inhibitors
Distribution category	POM
Country of origin	India
Associated product	GINIB 100 film coated tablets
Marketing Authorization Holder	Cipla Ltd Cipla House, Peninsula Business Park, GanpatraoKadam Marg, Lower Parel, Mumbai 400 013, India.
Local Technical Representative	Salama Pharmaceuticals limited, 13/19, Uhuru Nyamwezi street, P. O. Box 65235, 13/19 Aggrey St Dar es Salaam Tanzania.

1.2 Assessment procedure

The application for registration of Darunavir was submitted on 05 June 2018. The product underwent abridged assessment. Assessment was completed in 2 (two) rounds of evaluation and the product was registered on 26 November 2021.

1.3 Information for users

Visual description of the finished product	Light orange coloured, oval shaped, biconvex, film coated tablet, debossed with ‘DNV’ on one side and ‘400’ on other side.

Primary packing material	Opaque, white, 85cc high density polyethylene (HDPE) plastic bottle
Secondary packing materials	None
Shelf-life and storage condition	24 months, Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).
Route of administration	Oral
Therapeutic indications	Darunavir tablets, co-administered with ritonavir (darunavir/ritonavir), in combination with other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus (HIV-1) infection in adult and pediatric patients 3 years of age and older or weighing ≥15 kg. Darunavir tablets, co-administered with ritonavir (darunavir/ritonavir), in combination with other antiretroviral agents, is indicated for the treatment of human immunodeficiency virus (HIV-1) infection in adult and pediatric patients 3 years of age and older.

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: N/A

Composition: N/A

Pack size:N/A

Manufacturing details: N/A

Storage conditions: N/A

Manufacturer address: N/A

Unique identifier: Not applicable

Special warnings/precautions or instructions for use: N/A

The details of the primary pack include:

Brand name and strength: Darunavir (Each film coated tablet contains: Darunavir ethanolate equivalent to Darunavir 400 mg)

Manufacturing details: batch number, manufacturing date and expiry date

Name of manufacturer: Cipla Ltd
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.

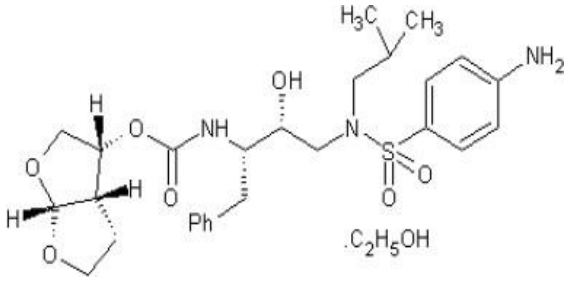
General Information

Darunavir ethanolate API is non-compendia.

Molecular formula: $C_{27}H_{37}N_3O_7S.C_2H_5OH$

Chemical name:
[[(1S, 2R)-3-[[(4-aminophenyl) sulfonyl] (2-methylpropyl) amino]-2-hydroxy-1-(phenylmethyl) propyl]-carbamic acid (3R,3aS,6aR)-hexahydrofuro[2,3-b] furan-3-yl ester monoethanolate

Structure:



General properties

The active substance is a white to pale yellow colour slightly hygroscopic solid, freely soluble in
dichloromethane, very slightly soluble in ethyl alcohol absolute and practically insoluble in water.

Darunavir is poorly soluble substance according to the BCS is a class II substance, hence particle size distribution (PSD) and polymorphism are considered critical parameters and form part of the FPP manufacturer's API specifications. The API exhibits polymorphism and exists as ethanolate, hydrate, and amorphous forms, under commercial synthesis conditions, Darunavir is isolated as a ethanolate. The capability of the analytical methods used to discriminate the potential polymorphs has been demonstrated, and batch analysis data confirm that the manufacturing process used consistently produces the same polymorphic form. The acceptance criterion for PSD is based on that used in the manufacture of the bio-batch and is acceptable.

Manufacture

Darunavir ethanolate API manufacturer is Cipla Limited, Manufacturing Division, Plot No.: D-7-Bulk Drug II block &At Plot D27- API I Block, MIDC Industrial Area, Kurkumbh Village Taluka- Daund, District- Pune, Maharashtra - 413802 India. The manufacturing complies with GMP requirements as evidenced by the GMP certificate issued by the Food & Drug Administration, Maharashtra State, India. Darunavir ethanolate 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 (visual inspection), solubility, identity (IR and HPLC), polymorphism (IR), specific optical rotation, residual of ignition, assay (HPLC), related impurities (HPLC), residual solvents (GC), water content (KF), heavy metals, ethanol content (GC), and particle size (laser diffraction). Compliance to these specifications were established via batch analysis data and stability studies.

<u>Stability and container closure system</u>

The re-test period of Darunavir ethanolate API is 24 months when packed in double clear polythene bags enclosed in Triple laminated high barrier bag and hermetically sealed, placed in fiber drum with storage condition 'Store the material at controlled room temperature (15°C to 30°C)'.

Quality of the Finished Pharmaceutical Product

Formulation

Darunavir is a light orange coloured, oval shaped, biconvex, film coated tablet, debossed with 'DNV' on one side and '400' on other side.

Darunavir contains the Darunavir ethanolate and other ingredients listed here after: Silicified Microcrystalline cellulose, Crospovidone, Colloidal silicon dioxide, Magnesium Stearate, Purified Water, Opadry II Orange 85F530009 (Polyvinyl Alcohol, Titanium Dioxide, Macrogol/PEG, Talc, FD&C Yellow #6/Sunset Yellow FCF Aluminium Lake), and Opadry II Orange 85F530027(Polyvinyl Alcohol, Titanium Dioxide, Macrogol/PEG, Talc, FD&C Yellow #6 / Sunset Yellow FCF Aluminium Lake). The quantities of all ingredients are confirmed to be in line with the recommendations of Handbook of Pharmaceutical Excipients, 8^{th} Edition in terms of function and quantities.

Manufacture

The finished product manufacturer is Cipla limited (Patalganga Unit II), Plot No. A-42, MIDC, Patalganga-410220, Dist. Raigad, Maharashtra, India. The compliance of the site to TMDA GMP standards was confirmed through site inspection on 25 May 2018. Current the certificate was already expired and the applicant has already applied for re-inspection.

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: visual description, identification of API (HPLC and UV), average weight, assay (HPLC), uniformity of dosage (weight variation), related substances (HPLC), disintegration, dissolution (Ph. Eur), water content (K.F), identification of colorants, uniformity of weight, ethanol content (GC), polymorphic identification (IR), and microbiological quality. Compliance to the standard was established using batch analysis data and stability data.

Stability and container closure system

Stability studies were conducted on a 2 (two) batches of the finished product stored at 30 ± 2°C & RH: 75 ± 5% RH for 36 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 high density polyethylene (HDPE) plastic bottle with storage condition 'Store at controlled room temperature of 25°C (77°F), Excursions permitted 15° to 30°C (59° to 86° F).'.

Safety and efficacy information

The biowaiver was approved based on additional strength.

Darunavir fulfilled the criteria for waiving an in-vivo bioequivalence study as per relevant TMDA guidance. Dissolution profiles of lower strength - Darunavir 400 mg film-coated tablets was compared to Darunavir 600 mg film-coated tablets. Less than 85% of the labelled amount of Darunavir had dissolved in all three media. Therefore, necessitating calculation of similarity factor f2, which was noted to be above 50.

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. Darunavir 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

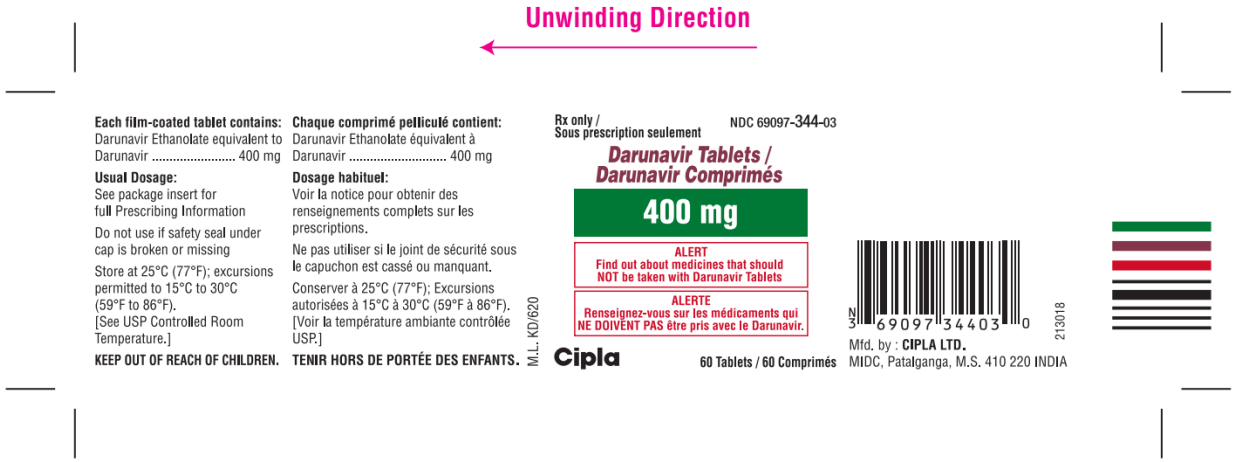
Application for renewal of registration was submitted on <DDMMYYYY>. The application was finalized in <number> rounds of evaluation. The product was confirmed to still be compliant to the standards of quality, safety and efficacy, hence registration was renewed on <DDMMYYYY>.

PART 5: CHANGE HISTORY

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

Annex I: Mock up labels;

Primary pack label;



Effective date: 03/10/2022