THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR DARUNAVIR ETHANOLATE 800 MG AND RITONAVIR 100MG FILM COATED TABLETS

Version number 01, 03/01/2023

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1. Introduction

Darunavir/Ritonavir tablets is an antiretroviral fixed dose bilayer formulation of the individual components that make up of Darunavir ethanolate and Ritonavir that has activity against HIV-1 that can be considered as generic combination of Prezista® (darunavir) tablet 800 mg of Janssen Ortho LLC, Gurabo, PR 00778 and Norvir® (ritonavir) tablet 100 mg of Abbvie Inc. North Chicago, IL 60064 USA.

Darunavir is an inhibitor of the dimerisation and of the catalytic activity of the HIV-1 protease. It selectively inhibits the cleavage of HIV encoded Gag-Pol polyproteins in virus infected cells, thereby preventing the formation of mature infectious virus particles. Pharmacokinetic enhancement by ritonavir is based on its potent inhibition of CYP3A- mediated metabolism. The degree of enhancement is related to the metabolic pathway of the co administered protease inhibitor and the impact of the co-administered protease inhibitor on the metabolism of ritonavir. Darunavir/Ritonavir tablets is approved in Tanzania for use in combination with other antiretroviral medicines for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and adolescents weighing at least 40 kg.

1.1 Product details

Registration number	TAN 21 HM 0402
Brand name	Darunavir/Ritonavir
Generic name, strength and form	Darunavir (as ethanolate) / Ritonavir 800mg /100mg tablets
ATC classification	Antivirals for systemic use, protease inhibitors (darunavir: J05AR14, ritonavir: J05AE03)
Distribution category	POM
Country of origin	India
Associated product	Darunavir and Ritonavir Tablets 400mg/50mg
Marketing Authorization Holder	Hetero Labs Limited, 7-2-A2, Hetero Corporate, Industrial Estates, Sanath Nagar, Hyderabad-500 018. Telangana state, India.
Local Technical Representative	Kas Medics Limited, Umoja Complex Plot No.11, Vingunguti Industrial Area Along Nyerere Road, Dar-Es-Salaam, Tanzania.

1.2 Assessment procedure

The application for registration of Darunavir/Ritonavir tablets was submitted on 23/07/2021. The product underwent full assessment. Assessment was completed in 2(two) rounds of evaluation. Darunavir/Ritonavir tablets was registered on 09/10/2021.

1.3 Information for users

Visual description of the finished product	yellow, capsule shaped, bevel edged, biconvex film coated tablets debossed with 'H' on one side and 'D46' on the other side
Primary packing material	60’s and 180’s count HDPE bottles
Secondary packing materials	N/A
Shelf-life and storage condition	24 months, Do not store above 30°C. Keep container tightly closed, dispense in original container
Route of administration	Oral
Therapeutic indications	Indicated in combination with other antiretroviral medicines for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults and adolescents weighing at least 40 kg

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 that is intended for long term use, the package insert contains both full prescribing information as per SmPC and simplified information for patients.

Container labels

The product label information is presented in English. Details in the secondary pack label include:

Brand name: Darunavir/Ritonavir

Composition: Each Film-Coated tablet contains 867.28 mg of Darunavir Ethanolate equivalent to 800 mg of Darunavir and Ritonavir 100 mg

Pack size: 60’s and 180’s tablets

Manufacturing details: batch number, manufacturing date, expiry date

Storage conditions: Do not store above 30°C. Keep container tightly closed, dispense in original container

Manufacturer address: Hetero Labs Limited, Unit III, 22-110, IDA, Jeedimetla, Hyderabad, Telangana, India.

Unique identifier: N/A

Special warnings/precautions or instructions for use: Find out about medicines that should NOT be taken with Darunavir and Ritonavir. Note to pharmacist: Do not cover ALERT box with pharmacy label

The details of the primary pack include:
Brand name and strength: Darunavir/Ritonavir
Manufacturing details: batch number, manufacturing date, expiry date
Name of manufacturer: Hetero Labs Limited

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 quality of the APIs was submitted in form of Full details.

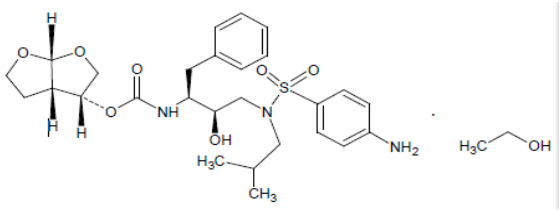
Darunavir ethanolate

General properties
Darunavir ethanolate API is non-compendia.

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

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

Structure:



Critical physico-chemical properties are:

Darunavir ethanolate is an off-white to cream colour hygroscopic powder. The structure and absolute configuration have been confirmed with single crystal X-ray crystallography. The manufacturer consistently produces crystalline polymorphic form A, which is routinely controlled by XRD in the specifications of the API.

Darunavir is poorly soluble substance according to the BCS is a class II substance, therefore control of polymorphism and particle size is considered critical. The control of particle size

distribution was demonstrated in the API specifications. The PSD limits are based on the results obtained for the API batch used in the manufacture of the FPP biobatch.

Manufacture

The API manufacturing site, Hetero Labs Limited, Unit-IX, Plot No.2, Hetero Infrastructure SEZ Ltd., N. Narasapuram (Village), Nakkapalli (Mandal), Visakhapatnam District - 531 081, Andhra Pradesh, INDIA. was noted to comply with WHO GMP requirements as evidenced by the GMP certificate issued by Drugs Control Administration of Andhra Padesh, 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, solubility, identification (IR, HPLC and XRPD), water content (KF), residue on ignition, related substances (HPLC), ethanol content (GC), assay (HPLC), residual solvents (GC), specific optical rotation and particle size distribution (PSD). Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Darunavir ethanolate API is 30 months when packed in stored in the original packing material and stored at in a refrigerator (2 °C to 8 °C), protect from light, protect from moisture.

Ritonavir

General properties

Ritonavir API is described in the Ph. Int, Ph. Eur, and USP.

Molecular formula: $C_{37}H_{48}N_6O_5S_2$

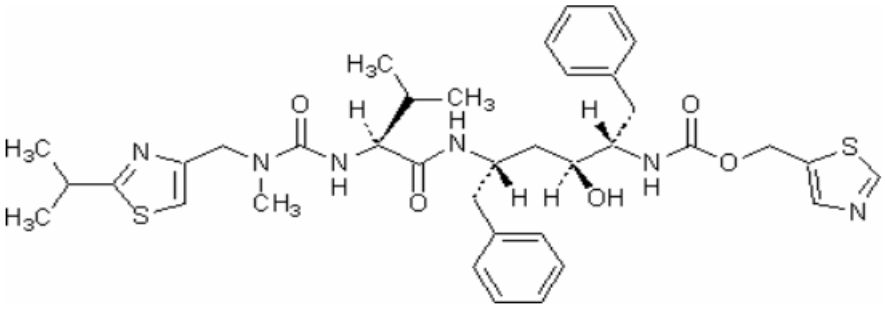
Chemical names:

i) 2, 4, 7, 12-Tetraazatridecan-13-oic acid, 10-hydroxy- 2- methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4- thiazolyl]-3,6- dioxo-8,11-bis (phenyl methyl)-5- thiazolymethyl ester [5S- (5R*,8R*,10R*,11R*)]

ii) 5-Thiazolylmethyl [(αS)- α-[(1S,3S)-1-hydroxy-3- [(2S)-2-[3- [(2-isopropyl-4-thiazolyl)methyl]-3- methylureido]-3- methyl butyramido] -4 phenyl butyl] phenethyl] carbamate

iii) Thiazol-5-ylmethyl[(1S,2S,4S)-1-benzyl-2-hydroxy-4- [[(2S)-3- methyl-2-[[methyl[[2-(1-methylethyl) thiazol- 4-yl] methyl] carbamoyl] amino] butanoyl] amino]-5 phenylpentyl] carbamate

Structure:



Critical physico-chemical properties are:

The API has four chiral centres, is practically insoluble in water and is known to exhibit polymorphism, with various crystal forms. The manufacture of ritonavir entails several steps and stereo selectively produces the desired stereoisomer. Polymorphic form II, characterised by the XRPD pattern, is consistently produced.

Ritonavir is a BCS class IV compound (low solubility and low permeability), nevertheless the polymorphic form and particle size distribution of the active substance are not considered critical quality attributes for the tablet formulation since the active substance undergoes a hot melt extrusion process and is rendered amorphous during the finished product manufacturing process.

Manufacture

The API manufacturing site, Hetero Labs Limited, Unit-IX, Plot No.2, Hetero Infrastructure SEZ Ltd., N. Narasapuram (Village), Nakkapalli (Mandal), Visakhapatnam District - 531 081, Andhra Pradesh, INDIA. was noted to comply with WHO GMP requirements as evidenced by the GMP certificate issued by Drugs Control Administration of Andhra Padesh, India. Ritonavir 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 USP, in-house standards and ICHQ3A. The parameters monitored during quality control are: description, solubility, identification (IR, HPLC), polymorphic form (XRPD), water content (KF), residue on ignition, related substances (HPLC), assay (HPLC), specific optical rotation, residual solvents (GC), microbial limit. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Darunavir ethanolate API is 12 months when packed in stored in the original packing material and stored at 25ºC, excursions permitted between 15ºC and 30ºC.

Quality of the Finished Pharmaceutical Product

Formulation

Darunavir/Ritonavir tablets is a yellow, capsule shaped, bevel edged, biconvex film coated tablets debossed with 'H' on one side and 'D46' on the other side.

Darunavir/Ritonavir tablets contains Darunavir ethanolate and Ritonavir and other ingredients listed here after: crospovidone, hypromellose 5 cps, silicified microcrystalline cellulose, copovidone, colloidal silicon dioxide, magnesium stearate, sorbitan monolaurate, dibasic calcium phosphate anhydrous, dibasic calcium phosphate dihydrate, microcrystalline cellulose, corn starch, mannitol, sodium stearyl fumarate, purified water, HPMC 2910/ hypromellose 6 cP, titanium dioxide, macrogol/peg 400, HPMC 2910/Hypromellose 15 cP, hydroxypropyl cellulose, iron oxide yellow, talc, macrogol/peg 3350, colloidal anhydrous silica, polysorbate 80. The quantities of all ingredients are confirmed to be in line with the recommendations of Handbook of Pharmaceutical Excipients, Edition 8^{th} in terms of function and quantities.

Manufacture

The finished product was manufactured at Hetero Labs Limited, Unit III,22-110, IDA,Jeedimetla, Hyderabad, Telangana, INDIA.The compliance of the site to TMDA GMP standards was confirmed through site inspection on 02/07/2020.

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, identification of APIs (TLC and HPLC), average weight, water content (KF), dissolution (HPLC detection), uniformity of dosage units (content uniformity), related substances (HPLC), assay (HPLC), and microbial limits. Compliance to the standard was established using batch analysis data and stability data.

Stability and container closure system

Stability studies were conducted on three (3) batches of the finished product stored at 30^0 ± 2°C & 75% ± 5% RH for 24 months and 40^0 ± 2°C & 75% ± 5% RH for 6 months. Based on the stability data presented, the approved shelf-life is 24 months when stored in HDPE bottles at Do not store above 30°C. Keep container tightly closed, dispense in original container.

Safety and efficacy information

Safety and efficacy of Darunavir/Ritonavir tablets was established through bioequivalence trial.

BE trial report number BE/19/100 was submitted.

In case of BE:

Study title	An open-label, balanced, randomized, two treatments, two sequence, two period, two way cross-over, single oral dose bioequivalence study of Darunavir and Ritonavir Tablets 800 mg/100 mg of Hetero Labs Limited, India with PREZISTA® (darunavir) tablets 800 mg of Janssen Therapeutics, NJ 08560 and Norvir® (Ritonavir) Tablets 100 mg of AbbVie Inc., USA, in normal, healthy, adult, human subjects under fed conditions.
Study design	An open-label, balanced, randomized, two treatments, two sequence, two period, two way cross-over, single oral dose bioequivalence study under fed condition
Study sites	Clinical facility: Raptim Research Ltd., PAP-213 (Screening Facility), A-226, (Clinical Pharmacology Unit), T.T.C., Industrial Area, Mahape M.I.D.C., Navi Mumbai - 400 701, India. Clinical Laboratories: Raptim Research Ltd., Clinical Pharmacology Unit (A-226), T.T.C. Industrial Area, Mahape M.I.D.C., Navi Mumbai – 400701, India. and Clinitech Laboratory Pvt. Ltd. Shop No. 9,10,11,12, Dattatray Maharaj CHS, 1st floor, Janta Sahakari Bank, Plot No. 6, Sector 8, Airoli, Navi Mumbai, Maharashtra. Analytical Laboratories, Pharmacokinetic/statistical analysis: Raptim Research Ltd., Bioanalytical Unit: A-242,

	T.T.C., Industrial Area, Mahape M.I.D.C., Navi Mumbai - 400 701, India.	
Study dates	Screening 27/05/19-14/06/19 Clinical 15/06/19-26/06/19 Bioanalysis 05/07/19-18/07/19 Pharmacokinetic and Statistics 23/07/19-26/07/19	
Primary objective	To assess whether the test product is bioequivalent to reference product	
Secondary objective	To assess safety and tolerability profile of test and reference products	
Number of participants	A total of 54 (52 male and 02 female), normal, healthy, adult, human subjects were enrolled in the study but one subject was terminated from the study due to adverse event after 10.00 hours post-dose blood sample collection in period I. 54 subjects were analyzed according to protocol but only 53 subjects who completed the study were included in the statistical calculation	
Monitored parameters	Tmax, Cmax, AUC0→t, AUC0→∞, AUC% Extrapolation Kel and T1/2	
Investigational medicinal products	Test Product	Reference products
	Strength: 800 mg/100 mg Batch number: E182176A Expiry date: 07/2020	Strength: 800 mg/100 mg Batch numbers: Darunavir: 17NG996 Ritonavir: 1089793 Expiry dates: 06/2019 and 02/07/2019
Analytical method	LC-MS/MS method was used for the determination of plasma concentration of analyte	
Statistical method	Statistical Analysis Software SAS® (SAS Institute Inc., USA) Version 9.4	

Efficacy results are summarized as follows:

Darunavir:

Parameter	Test	Reference	% Ratio of geometric means	90 % Confidence interval	DF	CV (%)
AUC0-t (hr.ng/mL)	86819.09	88271.00	98.36	91.82-105.36	51	21.38
C_{max} (ng/mL)	8084.73	7887.28	102.50	97.32-107.97	51	16.05

Ritonavir:

Parameter	Test	Reference	% Ratio of Geometric Means	90 % Confidence Interval	DF	CV (%)
AUC0-t (hr.ng/mL)	5048.50	5313.94	95.00	88.29-102.23	51	22.81
C_{max} (ng/mL)	737.48	742.05	99.38	90.71-108.89	51	28.62

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, Darunavir/Ritonavir tablets is equivalent and interchangeable with PREZISTA® (darunavir) tablets 800 mg of Janssen Therapeutics, NJ 08560 and Norvir® (Ritonavir) Tablets 100 mg of AbbVie Inc., USA under acceptable in vivo experimental conditions.

4. Benefit-Risk Assessment and Conclusion

On basis ofthe 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/Ritonavir tablets 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 label

Primary labels:

Size: 130x60 mm

Colours: 5

- Pantone Black C
- PANTONE 485 C
- PANTONE 1817 C
- PANTONE 2766 C
- PANTONE Green C

Size: 180x65 mm

Colours: 5

- Pantone Black C
- PANTONE 485 C
- PANTONE 1817 C
- PANTONE 2766 C
- PANTONE Green C

Secondary label

N/A