THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR ALLTERA 50 (LOPINAVIR 40 MG AND RITONAVIR 10 MG) ORAL GRANULES

Version number 1
05 January, 2022

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1. Introduction

ALLTERA 50 is a generic medicine of Kaletra (Lopinavir/Ritonavir) Oral Solution 80 mg/ 20 mg by AbbVie Ltd is an antiretroviral medicinal product. Both active substances in ALLTERA 50 are protease inhibitors: they block an enzyme called protease that is involved in the reproduction of HIV. When the enzyme is blocked, the virus does not reproduce normally slowing down its multiplication in the body. In ALLTERA 50, Lopinavir provides the activity against the virus while ritonavir mainly works as a 'booster' to slow down the rate at which Lopinavir is broken down by the liver. ALLTERA 50 does not cure HIV infection or AIDS, but it may hold off damage to the immune system, and the development of infections and diseases associated with AIDS. ALLTERA 50 is approved in Tanzania for use in infants and children patients14 days and older, weighing over 3 kg.

1.1.Product details

Registration number	TAN 22 HM 0028
Brand name	ALLTERA 50
Generic name, strength, and form	Lopinavir 40 mg Ritonavir 10 mg
ATC classification	ATC code: J05AR10 – Protease inhibitors
Distribution category	POM
Country of origin	India
Associated product	N/A
Marketing Authorization Holder	Mylan Laboratories Limited Address: Plot No. 564/A/22, Road No. 92, Jubilee Hills, Hyderabad - 500096, Telangana, INDIA. E-Mail: Kulbhushan.Ganotra@mylan.in
Local Technical Representative	Synermed Pharmaceuticals (Tanzania) Limited Address: Plot No 31132, Makaburini, Nyerere road, Dar- es- salaam, Tanzania E-mail: info(Esvnermedtz.com)

1.2.Assessment procedure

The application for registration of ALLTERA 50 was submitted on 15 April 2021. The product underwent abridge assessment. Assessment was completed in 2 (two) rounds of evaluation and the product was registered on 10 January 2022.

1.3.Information for users

Visual description of the finished product	A white to creamish granular powder filled in sachet
Primary packing material	Sachet pack comprises of printed triple laminated roll with AL foil, soft, dull side PET and bright side laminated to PE film
Secondary packing materials	A printed carton box
Shelf-life and storage condition	24 months, do not store above 30^{o}C. Store in original container
Route of administration	Oral
Therapeutic indications	Lopinavir/Ritonavir Granules 40 mg/10 mg is indicated for the treatment of HIV-1 infected children in combination with other antiretroviral agents

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: ALLTERA 50

Composition: Lopinavir 40 mg, Ritonavir 10 mg

Pack size: 120 sachets

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

Storage conditions: Do not store above 30^{o}C. Store in original container

Manufacturer address: physical address of release site

Unique identifier: Not applicable

Special warnings/precautions or instructions for use: This medicine contains mannitol (583 mg per sachet). Not to exceed prescribed dosage, read the package leaflet before use.

The details of the primary pack include:

Brand name and strength: ALLTERA 50

Manufacturing details: batch number, manufacturing date and expiry date

Name of manufacturer: Mylan Laboratories 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 the quality of the APIs was submitted in form of DMFs.

Lopinavir:

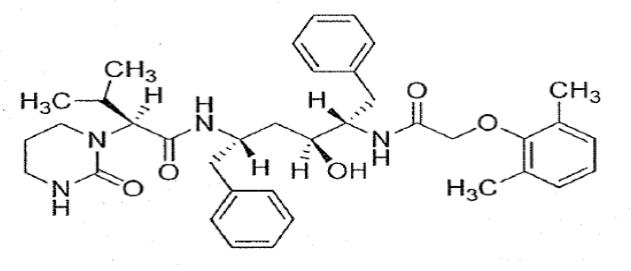
General Information

Lopinavir API is compendia in USP, BP/Ph.Eur., and International Pharmacopeia.

Molecular formula: $C_{37}H_{48}N_4O_5$

Chemical name:
(2S)-N-[(1S,3S,4S)-1-Benzyl-4-[[2-(2,6-dimethylphenoxy) acetyl]-amino]- 3-hydroxy-5-phenylpentyl]-3-methyl-2-[2-oxotetrahydropyrimidin-1(2H)-yl] butanamide

Structure:



General properties

Lopinavir is a white or yellowish-white, slightly hygroscopic powder, practically insoluble in water. Polymorphism has been observed for active substance. Batch analysis data provided confirmed that the active substance manufacturer consistently produces the same form (Type-I higher hydrate form).

Manufacture

Lopinavir API manufacturers are Mylan Laboratories Limited (Unit 1), Survey No. lOl42, Gaddapotharam, Kazipally Industrial Area, Medak District-502319, Telangana, India, Mylan Laboratories Limited (Unit 2), Survey No. IOl42, Gaddapotharam, Kazipally Industrial Area, Medak District-502319, Telangana, India, and Sionc Pharmaceuticals Pvt.Ltd, Plot. 34A, Road No'1, JN Pharma City, IDA Parawada, Thanam {V), Visakhapatnam – 531021, Andhra Pradesh, India. The manufacturing complies with GMP requirements as evidenced by the GMP certificates issued by the WHO. Lopinavir 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 standards and ICHQ3A. The parameters monitored during quality control are: Description, Solubility, Identification (IR and HPLC), Water content (KF), Residual of ignition, Heavy metal, Specific rotation, Related substances (HPLC), Assay (By HPLC), and Residual solvents (GC). Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Lopinavir API is 36 months when packed in translucent polyethylene bag (LDPE) (purged with nitrogen) with storage condition ‘Store in well-closed containers below 30°C, protect from moisture’.

Ritonavir:

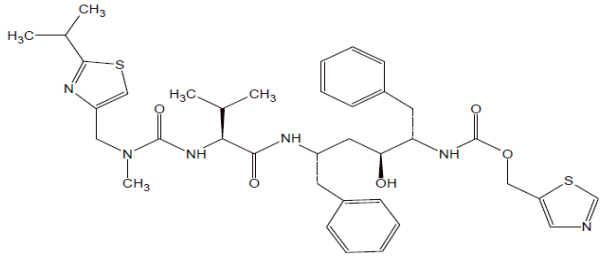
General Information

Ritonavir API is compendia in USP, BP/Ph.Eur., and International Pharmacopeia.

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

Chemical name:
(5S,8S,10S,11S)-10-Hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1- methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid 5-hiozolylmethyl ester

Structure:



General properties

Ritonavir is a white or almost white powder, practically insoluble in water. Polymorphism has been observed for active substance and is controlled by a XRD identification test in the active substance specifications. Batch analysis data provided confirmed that the active substance manufacturer consistently produces the same form (Form-II).

Manufacture

Ritonavir API manufacturers are Mylan Laboratories Limited (Unit-8), G. Chodavaram, Poosapatirega Mandal, Vizianagaram District – 535204, Andhra Pradesh, India, and Sionc Pharmaceuticals Pvt.Ltd, Plot. 34A, Road No.1, JN Pharma City, IDA Parawada, Thanam (V), Visakhapatnam – 531021, Andhra Pradesh, India. The manufacturing complies with GMP requirements as evidenced by the GMP certificates issued by the WHO. 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 standards and ICHQ3A. The parameters monitored during quality control are: Description, Solubility, Identification (IR and HPLC),

Water content (KF), Residual of ignition, Heavy metal, Specific rotation, Related substances (HPLC), Assay (HPLC), Residual solvents (GC), 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 Ritonavir API is 60 months when packed in antistatic white low-density polyethylene (LDPE) bag under nitrogen atmosphere with storage condition 'Preserve in tight, light resistant containers and store between 5°C and 30°C'.

Quality of the Finished Pharmaceutical Product

Formulation

ALLTERA 50 is a white to creamish granular powder filled in sachet.

ALLTERA 50 contains the Lopinavir and Ritonavir, and other ingredients listed here after: Copovidone, sorbitan monolaurate, colloidal silicon dioxide, ethyl cellulose, mannitol, acesulfame potassium, sodium stearyl fumarate and vanilla flavour (Flavoring substances, Natural flavoring substances, Flavoring preparations, Maize maltodextrin, Modified corn starch E 1450, Glyceryl triacetate E1518). 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 manufacturer is Mylan Laboratories Limited, Plot No. 11, 12 & 13, Indore Special Economic Zone, Pharma Zone, Phase-II, Sector- III, Pithampur - 45 47 7 5 Dist. Dhar, MadhYa Pradesh, India. The compliance of the site to TMDA GMP standards was confirmed through site inspection on 23 September 2019.

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 (visual), the identity of API (HPLC and TLC), Average weight of tablet, Water content (By KF), Uniformity of Dosage units (content uniformity), Dissolution (HPLC), Related substances (HPLC), Assay (HPLC), Microbial enumeration tests, and Test for specified Microorganisms. 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 sachet pack comprises of printed triple laminated roll with Aluminium foil, soft, dull side PET and bright side laminated to PE film with storage condition 'Do not store above 30'C. Store in original container'.

Safety and efficacy information

Safety and efficacy of ALLTERA 50 was established through a bioequivalence trial.

BE trial report number C16212 was submitted.

Study title	A randomized, open-label, balanced, two-treatment, two-period, two-sequence, single-dose, crossover oral bioequivalence study of Lopinavir/Ritonavir Granules (2 Sachets X 40110 mg) 40 mg / l0 mg of Mylan Laboratories Limited, India Versus KALETRA with lopinavir/Ritonavir) Oral Solution 80 mg / 20 mg per mL of AbbVie Inc., North Chicago. IL 60064 USA, in normal healthy adult human subjects under fed conditions
Study design	An open label, randomized, two-treatment, two-sequence, two-period, crossover, single dose bioavailability study in 72 healthy, adult, human subjects under fed conditions.
Study site	Aizant Drug Research Solutions Pvt. Ltd, Survey No.: 172 and 173, Apparel Park Road, Dulapally Village. Quthbullapur Mandal, Hyderabad, India.
Study dates	17 May 2017 - 29 July 2017
Primary objective	To evaluate the oral bioequivalence of Lopinavir/Ritonavir Granules (2 Sachets X 40/10 mg) 40 mg / 10 mg of Mylan Laboratories Limited, India with KALETRA® (Lopinavir/ Ritonavir) Oral Solution 80 mg / 20 mg per mL of AbbVie Inc., North Chicago, IL 60064 USA, in normal healthy adult human subjects under fed conditions
Secondary objective	To monitor the adverse events and to ensure the safety of the subjects
Number of participants	Subjects Enrolled: 72 Total number of subjects completed the study: 68 Drop-out / withdrawn: 4 Included subjects in statistical analysis: 68

Monitored parameters	Tmax, Cmax, AUC0→t, AUC0→∞, AUC% Extrapolation Kel and T1/2	
Investigational medicinal products	Test Product	Reference product
	Strength: 40 mg / 10 mg Batch number: 2012897 Expiry date: October 2018	Strength: 80 mg / 20 mg per mL Batch number: 1043600 Expiry date: July 2017
Analytical method	LC-MS/MS method was used for the determination of plasma concentrations of analytes	
Statistical method	SAS Version 9.2 Software (SAS Institute Inc., USA)	

Efficacy results are summarized as follows:

For Lopinavir:

Parameter	Test	Reference	90 % Confidence interval	DF	CV (%)
Cmax (ng/mL)	389.809	369.967	94.15-117.91	66	40.9
AUC0-t (hr.ng/mL)	3144.695	2955.001	94.48-119.86	66	43.4
AUC0-inf (ng.hr/mL)	3215.917	3076.989	92.58-117.99	65	43.2

For Ritonavir:

Parameter	Test	Reference	90 % Confidence interval	DF	CV (%)
Cmax (ng/mL)	27.859	25.242	100.91-120.72	66	32.1
AUC0-t (hr.ng/mL)	219.562	202.972	98.53-119.94	66	35.4
AUC0-inf (ng.hr/mL)	226.160	208.668	98.36-119.42	66	34.9

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, Lopinavir/Ritonavir Granules (2 Sachets X 40/10 mg) 40 mg /10 mg of Mylan Laboratories Limited, India is equivalent and interchangeable with KALETRA with Lopinavir/Ritonavir Oral Solution 80 mg / 20 mg per mL of AbbVie Inc 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. ALLTERA 50 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 numbe	Date	Description of update	Section(s) Modified	Approval date

Annex I: Mock up labels