THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR ABACAVIR SULFATE/LAMIVUDINE 600 MG/ 300 MG FILM COATED TABLETS

Version number 1.0
21 August 2023

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1. Introduction

The product is a fixed combination contains Abacavir and lamivudine. Abacavir and lamivudine are NRTIs, and are potent selective inhibitors of HIV-1 and HIV-2 viruses. NRTIs are analogs of the natural substrates used to synthesize viral deoxyribonucleic acid (DNA), and they compete with them for incorporation into the growing viral DNA chain.

Both abacavir and lamivudine are metabolised sequentially by intracellular kinases to the respective 5'-triphosphates which are the active moieties. Lamivudine-TP and carbovir-TP (the active triphosphate form of abacavir) are substrates for and competitive inhibitors of HIV reverse transcriptase (RT). Their main antiviral activity is through incorporation of the monophosphate form into the viral DNA chain, resulting in chain termination. Abacavir and lamivudine triphosphates show significantly less affinity for host cell DNA polymerases.

Abacavir and lamivudine were shown to have additive antiretroviral activity with each other. The combination decreases number of HIV-1 RNA copies/ml, increases CD4 cell number/mm3 and slows down the CD8 cells number. This is demonstrated in several clinical trial. Abacavir Sulfate/ Lamivudine tablets is approved in Tanzania for use in HIV-1-infected adults, adolescents and children weighing at least 25 kg.

1.1 Product details

Registration number	TAN 23 H 0300
Brand name	Abacavir sulfate/ Lamivudine
Generic name, strength, and form	Each film coated tablet contains: Abacavir sulfate …….600 mg Lamivudine…… 300 mg
ATC classification	J05AR02 - Direct Acting antiviral for systemic use Lamivudine and Abacavir
Distribution category	POM
Country of origin	India
Associated product	N/A
Marketing Authorization Holder	Mylan Laboratories Limited Plot No. 564/A/22, Road No. 92, Jubilee Hills, Hyderabad, Telangana – 500 096, India
Local Technical Representative	Synermed Pharmaceuticals (Tanzania) Limited Plot No. 31/32 Makaburini, Nyerere road, Dar-es-salaam,

1.2 Assessment procedure

The application for registration of Abacavir sulfate/ Lamivudine was submitted on 07/10/2022. The product underwent abridged assessment. Assessment was completed in 2 (two) rounds of evaluation and the product was registered on 01 June 2023.

1.3 Information for users

Visual description of the finished product	Yellow colored, biconvex. film In-House coated tablet, debossed with "M157" on one side and plain on the other side
Primary packing material	HDPE bottle
Secondary packing materials	A printed carton box
Shelf-life and storage condition	36 months, Do not store above 30°C, store in the original container
Route of administration	Oral
Therapeutic indications	Abacavir and Lamivudine Tablets for Oral Suspension, in combination with other antiretroviral agents, are indicated for the treatment of HIV-1 infection

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: Abacavir Sulfate/ Lamivudine

Composition: Each film coated tablet contains:
Abacavir sulfate …….600 mg
Lamivudine…… 300 mg

Pack size: 30's tablets

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

Storage conditions: Do not store above 30°C, store in the original container

Manufacturer address: physical address of release site

Unique identifier: Not applicable

Special warnings/precautions or instructions for use: See enclosed leaflet

The details of the primary pack include:

Brand name and strength: Abacavir Sulfate/ Lamivudine 600 mg/ 300 mg

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.

Abacavir Sulfate

General Information

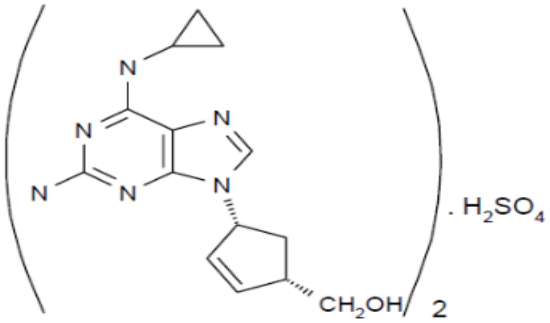
Abacavir Sulfate API is compendia in Ph.Int, USP, Ph.Eur., and BP.

Molecular formula: $C_{28}H_{38}N_{12}O_6S$

Chemical name:

Bis[[(1S,4R)-4-[2-amino-6-cyclopropylamino)-9H-purin-9- yl]cyclopent-2-enyl]methanol]sulfate

Structure:



General properties

Abacavir sulfate is white to off-white crystalline powder and the solubility is pH dependent with minimal solubility at basic pH and increased solubility at acid. This active substance is slightly soluble in diethyl ether and ethanol. Abacavir exhibits stereoisomerism due to the presence of two chiral centres (1S,4R absolute configuration). Enantiomeric purity is controlled routinely by

chiral HPLC. Abacavir produced by the proposed active substance supplier is a crystalline form. Polymorphism has not been found, although the active substance is of a crystalline nature.

Manufacture

Abacavir sulfate API manufacturers are Mylan Laboratories Limited (Unit-8), G Chodavaram, Poosapatirega Mandal, Vizianagaram District – 535204, Andhra Pradesh, India, and Mylan Laboratories Limited (Unit-10), Plot No. 86, Ramky Pharma City (India) Ltd, SEZ, JN Pharma City, Parawada Mandal, Visakhapatnam District – 531019, Andhra Pradesh, India. The manufacturing complies with GMP requirements as evidenced by the GMP certificate submitted. Abacavir sulfate 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, polymorphic identity (XRPD), content of sulfate, identification (IR, HPLC, and chemical), water determination, specific optical rotation, residue on ignition, organic impurities (HPLC), enantiomeric purity (HPLC), Assay (% w/w), residual solvents, and particle size (laser diffraction)). Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Abacavir sulfate API is 60 months when packed in low-density polyethylene (LDPE) bag with storage condition 'Store in air-tight container, protect from light at below 30^{o}C'.

A. <u>Lamivudine from Mylan Laboratories Limited</u>

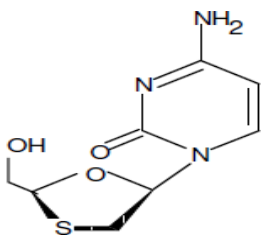
General Information

Lamivudine API is compendia in Ph.Int., USP, Ph.Eur., and BP.

Molecular formula: $C_8H_{11}N_3O_5S$

Chemical name:

2R-cis)-4-amino-1-(2R-hydroxymethyl-[1,3]oxathiolan-5S-yl)- 1H-pyrimidin-2-one
Structure:



General properties

Lamivudine is a white to off-white solid and soluble in water. This active substance exhibits also stereoisomerism due to the presence of two chiral centres (1S,4R absolute configuration). Enantiomeric purity is controlled routinely by chiral HPLC and specific rotation. Lamivudine may exist as either of two pseudopolymorphs (Form I or Form II). The manufacturing process of Lamivudine is well controlled to manufacture only Form II.

Manufacture

Lamivudine API manufacturers are Mylan Laboratories Limited (Unit-1), Survey No. 10/42, Gaddapotharam, Kazipally Industrial Area, Sangareddy District-502319, Telangana, India; Mylan Laboratories Limited (Unit-2), Survey No. 10/42, Gaddapotharam, Kazipally Industrial Area, Sangareddy District-502319, Telangana, India; Mylan Laboratories Limited (Unit-9), Plot No. 5, Road No.12, J.N. Pharma City, Tadi Village, Parawada Mandal, Visakhapatnam – 531021, Andhra Pradesh, India. The manufacturing complies with GMP requirements as evidenced by the GMP certificates submitted. Lamivudine 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, melting point, identification (IR and HPLC), light absorption, water determination (% w/w), limit of lamivudine enantiomer, other related compounds, residual solvent, assay, residue on ignition, melting range, specific optical rotation, bulk and tapped density, heavy metals, and particle size. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Lamivudine API is 60 months when packed in low-density polyethylene (LDPE) bag with storage condition ‘Store in air-tight container, protect from light at below 30^{o}C’.

B. Lamivudine from Hetero Labs Limited

General Information

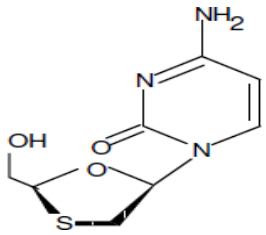
Lamivudine API is compendia in Ph.Int., USP, Ph.Eur., and BP.

Molecular formula: $C_8H_{11}N_3O_5S$

Chemical name:

2R-cis)-4-amino-1-(2R-hydroxymethyl-[1,3]oxathiolan-5S-yl)- 1H-pyrimidin-2-one

Structure:



General properties

Lamivudine is a white to off-white solid and soluble in water. This active substance exhibits also stereoisomerism due to the presence of two chiral centres (1S,4R absolute configuration). Enantiomeric purity is controlled routinely by chiral HPLC and specific rotation. Lamivudine may exist as either of two pseudopolymorphs (Form I or Form II). The manufacturing process of Lamivudine is well controlled to manufacture only Form II.

Manufacture

Lamivudine API manufacturer is Hetero Labs Limited, Unit-IX, Plot No.2, Hetero Infrastructure Limited –SEZ, N. Narasapuram (Village),Nakkapally (Mandal), Visakhapatnam District, Andhra Pradesh, India. The manufacturing complies with GMP requirements as evidenced by the GMP certificate submitted. Lamivudine 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, melting point, identification (IR and HPLC), light absorption, water determination (% w/w), limit of lamivudine enantiomer, other related compounds, residual solvent, assay, residue on ignition, melting range, specific optical rotation, bulk and tapped density, heavy metals, particle size, and tosilates content and mesylates content. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Lamivudine API is 60 months when packed in polyethylene bag with storage condition 'Preserve in tight, light resistant containers, store at 25ºC, excursions permitted between 15ºC and 30ºC'.

C. Lamivudine from Mylan Laboratories Limited

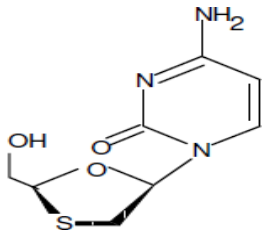
General Information

Lamivudine API is compendia in Ph.Int., USP, Ph.Eur., and BP.

Molecular formula: $C_8H_{11}N_3O_5S$

Chemical name:

2R-cis)-4-amino-1-(2R-hydroxymethyl-[1,3]oxathiolan-5S-yl)- 1H-pyrimidin-2-one
Structure:



General properties

Lamivudine is a white to off-white solid and soluble in water. This active substance exhibits also stereoisomerism due to the presence of two chiral centres (1S,4R absolute configuration). Enantiomeric purity is controlled routinely by chiral HPLC and specific rotation. Lamivudine may exist as either of two pseudopolymorphs (Form I or Form II). The manufacturing process of Lamivudine is well controlled to manufacture only Form II.

Manufacture

Lamivudine API manufacturers are Shanghai Desano Chemical Pharmaceutical Co., Ltd. (Abbreviated as Shanghai Desano), Block No: A16, B14, B15, L18 for process A (product code#: DBH010), B15, L18 for Process B (Product code#: DBH239), No.417 Binhai Road, Laogang Town, Pudong new Area, Shanghai 201302, China. The manufacturing complies with GMP requirements as evidenced by the GMP certificates submitted. Lamivudine 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, melting point, identification (IR and HPLC), light absorption, water determination (% w/w), limit of lamivudine enantiomer, other related compounds, residual solvent, assay, residue on ignition, melting range, specific optical rotation,

bulk and tapped density, heavy metals, and particle size. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Lamivudine API is 60 months when packed in low-density polyethylene (LDPE) bag with storage condition 'Preserve in well-closed, light resistant container at up to 30°C'.

Quality of the Finished Pharmaceutical Product

Formulation

Abacavir Sulfate/ Lamivudine tablets is a yellow colored, biconvex, film coated tablet, debossed with "M157" one side and plain on the other side.

Abacavir Sulfate/Lamivudine tablets contains the Abacavir Sulfate and Lamivudine, and other ingredients listed here after: Microcrystalline cellulose, Colloidal Silicon dioxide, Magnesium stearate, Sodium starch Glycolate, HPMC 2910/Hypromellose, Titanium dioxide, Macrogol/PEG 400, Iron Oxide Yellow, Polysorbate 80, FD&C Yellow #6/Sunset Yellow FCF Aluminum Lake, and Purified water. 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 Mylan Laboratories Limited, Plot No.11, 12 & 13, Indore Special Economic Zone, Pharma Zone, Phase-II, Sector-III, Pithampur - 454775, Dist. Dhar, Madhya Pradesh,India. The compliance of the sites to TMDA GMP standards was confirmed through site inspection on DD/MM/YYYY.

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 the APIs (HPLC, TLC), uniformity of dosage units, loss on drying, dissolution (HPLC detection), assay (by HPLC), organic impurities and microbiological examination of non-sterile products. 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 ± 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 36 months when stored in HDPE bottle with storage condition 'Do not store above 30°C, store in the original container'.

Safety and efficacy information

Cipla's Abacavir Sulfate/ Lamivudine tablets is already registered by WHO. Information on clinical data has been fully evaluated during the registration of the product. In this context, re-assessment of this part is not considered as necessarily required.

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. Abacavir Sulfate/ Lamivudine 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 labels;

Primary pack label;

Secondary pack label;