TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR INBEC TM (600 MG ABACAVIR (AS SULPHATE) + 50 MG DOLUTEGRAVIR (AS SODIUM)+ 300 MG LAMIVUDINE) FILM COATED TABLETS

Version number 0.1

March 2022

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1. Introduction

Inbec is a generic medicine of ViiV Healthcare UK Ltd's Triumeq. Inbec is an antiretroviral medicine belonging to J05AR – Antivirals for treatment of HIV, combinations group. Inbec activity is as follows: Dolutegravir inhibits HIV integrase which is essential for the HIV replication cycle. Abacavir and lamivudine are potent selective inhibitors of HIV-1 and HIV-2. Both are substrates for and competitive inhibitors of HIV reverse transcriptase (RT). However, 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. Inbec is approved in Tanzania for use in adults and adolescents above 12 years of age weighing at least 40 kg.

1.1 Product details

Registration number	TAN 21 HM 0039
Brand name	INBEC
Generic name, strength and form	600 Mg Abacavir (as Sulphate) + 50 Mg Dolutegravir (as Sodium)+ 300 Mg Lamivudine) Film Coated Tablets
ATC classification	J05AR – Antivirals for treatment of HIV, combinations
Distribution category	POM
Country of origin	India
Associated product	Not Applicable
Marketing Authorization Holder	Emcure Pharmaceuticals Limited, T-184, MIDC, Bhosari, Pune- 411026, India
Local Technical Representative	Phillips Pharmaceuticals (Tanzania)Limited Plot no.111, Nyerere Road, Vingunguti Industrial Area P.O. Box 737, Dar es Salaam.

1.2 Assessment procedure

The application for registration of Inbec was submitted on 22/03/2019. The product underwent abridged assessment. Assessment was completed in 2 rounds of evaluation. Inbec was registered on 24/12/2020.

1.3 Information for users

Visual description of the finished product	Light blue to blue, oval shaped, film coated tablets debossed with 'EM' on one side and "35" on another side.
Primary packing material	30 Tablets are packed in 120 cc white opaque HDPE bottle. 90 Tablets are packed in 250 cc white opaque HDPE bottle.
Secondary packing materials	Monocarton packed with 30 Tablets packed in 120 cc white opaque HDPE bottle or 90 Tablets packed in 250 cc white opaque HDPE bottle along with package insert.

Shelf-life and storage condition	24 months Store at or below 30°C. Store in the original package to protect from moisture.
Route of administration	Oral
Therapeutic indications	The Product, Abacavir 600 mg/Dolutegravir 50 mg/Lamivudine 300 mg Tablet is indicated for the treatment of HIV- 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 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: Inbec
Composition: 600 mg Abacavir (as Sulphate) + 50 mg Dolutegravir (as Sodium) + 300 mg Lamivudine) Film Coated Tablets
List of excipients:

1) Microcrystalline cellulose
2) Sodium Starch Glycolate
3) Povidone
4) Purified Water
5) Isopropyl Alcohol
6) Magnesium Stearate
7) Colorant

Pack size: 30 Tablets are packed in 120 cc white opaque HDPE bottle & 90 Tablets are packed in 250 cc white opaque HDPE bottle.

Manufacturing details: batch number, manufacturing date, expiry date

Storage conditions: Store at or below 30°C. Store in the original package to protect from moisture

Manufacturer address: Emcure Pharmaceuticals Limited, Plot No. P-1 & P-2, I.T.B Park, Phase II, M.I.D.C, Hinjawadi, Pune- 411 057, India
Unique identifier: TMDA registration number

Special warnings/precautions or instructions for use: Keep away from the reach of children

The details of the primary pack include:
Brand name and strength: Inbec

Manufacturing details: Space for printing was provided in the product label
Name of manufacturer: Emcure Pharmaceuticals 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 Ingredient(s)

1. Abacavir Sulfate

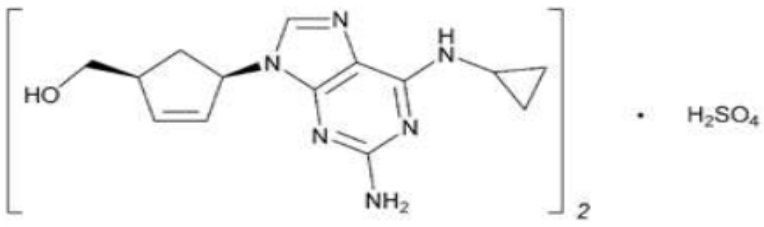
Information on quality of the API was submitted in form of proof WHO prequalification and the corresponding required information.

General properties
Artemether API is compendia in the US Pharmacopeia

Molecular formula: $[C_{14}H_{18}N_6O]$ 2. H_2SO_4

Chemical name: (1S,4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2- cyclopentene-1-methanol sulfate (salt) (2:1

Structure:



Critical physico-chemical properties of the API

Abacavir sulfate manufactured by Laurus Labs Limited shows two crystal form I and II of which polymorph form was confirmed by manufacturer. Laurus Labs Limited consistently produces same polymorphic form designated as Abacavir Sulfate crystalline Form II.

The API is practically insoluble in water thus, particle size is of critical concern, FPP manufacturer included test and limit for control of particles size has been included in the API specification

Manufacture
The API manufacturing site, Laurus Labs Limited plot No. 21, Jawaharlal Nehru Pharma City, Parawada, Visakhapatnam - 531 021 Andhra Pradesh, India was noted to comply with WHO GMP requirements as evidenced by the GMP certificate issued by Drugs Control Administration

(DCA), Andhra Pradesh. Abacavir 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 US Pharmacopeia standards, ICHQ3A and ICHQ3C. The parameters monitored during quality control are: description, solubility, identification, water content, sulphated ash, enantiomeric purity, related substances, particle size distribution, residual solvents and assay. Compliance to these specifications was established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Abacavir Sulphate API is 12 months when packed in transparent low density Polyethylene bag with strip seal followed by secondary pack with transparent low density Polyethylene bag with strip seal and finally kept in HDPE container and stored at or below 25℃ in well closed, light protected containers.

2. Dolutegravir Sodium

Information on quality of the API was submitted in form of proof WHO prequalification and the corresponding required information.

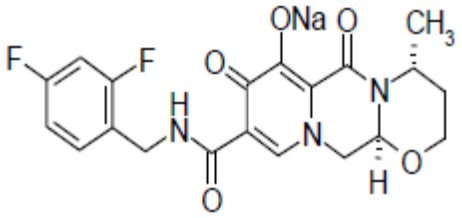
General properties

Dolutegravir Sodium API is compendia in US Pharmacopeia.

Molecular formula: $C_{20}H_{18}F_2N_3NaO_5$

Chemical name: Sodium (4R,12aS)-9-{[(2,4-difluorophenyl)methyl]carbamoyl}- 4- methyl-6,8-dioxo-3,4,6,8,12,12a-hexahydro-2H-pyrido[1',2':4,5] pyrazino[2,1-b][1,3]oxazin-7-olate.

Structure:



Critical physico-chemical properties of the API are:

Dolutegravir Sodium manufactured by Laurus Labs Limited is a white to pale yellow solid and exhibit polymorphism whereas the polymorphic form manufactured by Laurus Labs Limited was demonstrated as Form-1.

Dolutegravir is classified as either BCS class II or IV molecule, therefore control of polymorphism and particle size is considered critical. The control of particle size distribution was demonstrated in the API specification.

Manufacture

The API manufacturing site, Laurus Labs Limited plot No. 21, Jawaharlal Nehru Pharma City, Parawada, Visakhapatnam - 531 021 Andhra Pradesh, India was noted to comply with WHO GMP requirements as evidenced by the GMP certificate issued by Drugs Control Administration (DCA), Andhra Pradesh. Dolutegravir Sodium 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 US Pharmacopeia standards, ICHQ3A and ICHQ3C. The parameters monitored during quality control are: description, solubility, identification, water content, heavy metals, related substances, particle size distribution, residual solvents and assay. Compliance to these specifications was established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Dolutegravir Sodium API is 12 months when packed in transparent low density Polyethylene bag with strip seal followed by secondary pack with transparent low density Polyethylene bag with strip seal and finally kept in HDPE container and stored at or below 25℃ in well closed, light protected containers.

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3. Lamivudine

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

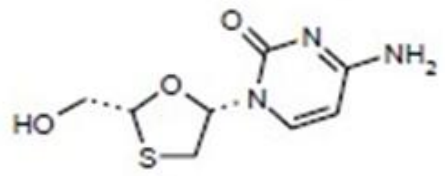
General properties

Lamivudine API is compendia in US Pharmacopeia

Molecular formula: $C_8H_{11}N_3O_3S$

Chemical name :): I. 2(1H)-Pyrimidinone,4-amino-1-[2- (hydroxyl methyl)-1,3-oxathiolan -5-yl]-, (2R-cis).

Structure:



Critical physico-chemical properties of the API are:

Lamivudine manufactured by Laurus Labs Limited is White to almost white solid soluble in water, sparingly soluble in methanol, slightly soluble to practically insoluble in ethanol and practically insoluble in acetone.and exhibit polymorphism whereas the polymorphic form manufactured by Laurus Labs Limited was demonstrated as Form-II and confirmed by XRD.

Lamivudine is classified as either BCS class I molecule and was demonstrated to have a very high aqueous solubility, therefore control of polymorphism and particle size is considered not critical. Nevertheless, particle size distribution was monitored on a routine basis as evidenced in the specification document.

Manufacture

The API manufacturing site, Laurus Labs Limited plot No. 18, Jawaharlal Nehru Pharma City, Parawada, Visakhapatnam - 531 021 Andhra Pradesh, India was noted to comply with WHO GMP requirements as evidenced by the GMP certificate issued by Drugs Control Administration (DCA), Andhra Pradesh. 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 US Pharmacopeia standards, ICHQ3A and ICHQ3C. The parameters monitored during quality control are: description, solubility, identification, light absorption, loss on drying, sulphated ash, heavy metals, and limit for Lamivudine Enantiomer, related substances, particle size distribution, residual solvents and assay. Compliance to these specifications was established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Lamivudine API is 24 months when packed in transparent low density Polyethylene bag with strip seal followed by secondary pack with transparent low density Polyethylene bag with strip seal and finally kept in HDPE container and stored at or below 25°C in well closed, light protected containers.

Quality of the Finished Pharmaceutical Product

Formulation

Inbec is a light blue to blue, oval shaped, film coated tablets debossed with 'EM' on one side and "35" on another side. Inbec contains Abacavir (as Sulphate), Dolutegravir (as Sodium) and Lamivudine and other ingredients listed here after:

1) Mannitol(2) (Pearlitol 25C)
2) Microcrystalline cellulose (Avicel PH 101)
3) Sodium Starch Glycolate (Primojel Type A)
4) Povidone (PVP K-30)
5) Purified Water
6) Isopropyl Alcohol and
7) Colourant

The quantities of all ingredients are confirmed to be in line with the recommendations of Handbook of Pharmaceutical Excipients, Edition 9th in terms of function and quantities.

Manufacture

The finished product was manufactured at Emcure Pharmaceuticals Ltd. Plot No.P-1, P-2. I.T.B.T Park, Phase II, M.I.D.C, Hinjwadi, Pune – 411 057, India. The compliance of the site to TMDA GMP standards was confirmed through site inspection on 09/04/2019.

Specifications

The FPP is non-compendial. The manufacturer controls the quality of the finished product as per in-house, ICHQ3C and ICHQ6A requirements. The parameters monitored during quality control are: description, identification, assay, dissolution, Uniformity of dosage units, related substances, water content, residual solvents and elemental impurities. Compliance to the standard was established using batch analysis data and stability data.

Stability and container closure system

Stability studies were conducted on three consecutive batches of the finished product stored at 30ºC ± 2 ºC /75%± 5% RH for 24 months and 40ºC ± 2/75% ±5% RH for 6 months. Based on the stability data presented, the approved shelf-life is 24 months when stored in HDPE container at or below 30ºC.

Safety and efficacy information

The product Inbec was assessed using an abridged review process; therefore, the data under this section was considered sufficient as submitted hence was not evaluated.

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. Inbec was recommended for registration.

5. Post-approval updates

Not Applicable

Feedback from pharmacovigilance, post marketing surveillance and enforcement activities

Type of feedback	Impact	Response
NA	NA	NA

Re-registration applications

NA

PART 5: CHANGE HISTORY

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

Annex I: Mock up label

Product Name	**INBEC Tablets (Non Royalty)**	**Sap code :**	**510009474IN02**	**Reference Artwork**	**510009474IN01**
Packaging Material	**Label**	**Reason of change :**	**Editorial changes**	**Proof 1**	**20.11.2018**
Size : Foil Width	----------	**Country :**	**General Export**		
Size : Foil Repeat Length	----------	**Pack Size :**	**30 T**		
Size : Strip Size	----------	**Barcode No. :**	**8902319031930**		
Size : PI - Open Size	----------	**Pharmacode :**	**2708**		
Size : Carton/Label	**L. 140 x H. 45 mm**	**No. of colours :**	**3**		
PM Style/Type :	----------	**Min. Font Size :**	**3.5 pt.**		
Remark (If any) :	----------			**Developed For :**	Emcure – Hinjawadi Ms. Ishwaja Dalvi

PANTONE 341 C **PANTONE Red 032 C** **Black**

52 mm | 54 mm | 52 mm | 54 mm

INBEC™
50/300/600 mg
Dolutegravir, Lamivudine
& Abacavir Tablets
Dolutégravir, Lamivudine
et Abacavir Comprimés

30 Tablets/
30 Comprimés

INBEC™

50/300/600 mg

Dolutegravir, Lamivudine
& Abacavir Tablets
Dolutégravir, Lamivudine
et Abacavir Comprimés

Emcure

Composition:
Each film coated tablet contains:
Dolutegravir sodium equivalent to Dolutegravir 50 mg
Lamivudine 300 mg
Abacavir Sulphate equivalent to Abacavir 600 mg
Titanium Dioxide and Indigo Carmine Aluminum Lake
Excipients Q.S
Composition:
Chaque comprimé pelliculé contient:
Dolutégravir sodique équivalent au Dolutégravir 50 mg
Lamivudine 300 mg
Sulfate d'Abacavir équivalent à Abacavir 600 mg
Dioxyde de titane, laque d'aluminium (carmin d'indigo)
Excipients Q.S

Store at or below 30°C. Store in the original package to protect from moisture.
Conserver à ou au-dessous de 30°C. Conserver dans l'emballage d'origine pour protéger de l'humidité.

Keep all medicines out of the reach of children.
Garder tous les médicaments hors de la portée des enfants.

See prescribing information for dosage information.
Voir les renseignements thérapeutiques pour les informations posologiques.

This product has been produced under a licence from the Medicines patent pool
Ce produit a été produit en vertu d'une licence de la Communauté de Brevets pour les médicaments

Any other use is not authorised
Toute autre utilisation n'est pas autorisée

WARNING: KEEP AWAY FROM THE REACH OF CHILDREN.
MISE EN GARDE: GARDER HORS DE LA PORTÉE DES ENFANTS.

30 Tablets/
30 Comprimés

INBEC™
50/300/600 mg
Dolutegravir, Lamivudine
& Abacavir Tablets
Dolutégravir, Lamivudine
et Abacavir Comprimés
Emcure

Mfg. Lic. No./Mfg. Lic. N°: [illegible]
Batch No./
Lot n°:
Mfg. Date/
Date de Fab.:
Exp Date/
Date d'Exp.:

Non Varnished Area
[illegible]

Non varnished area
Space for 2D Barcode
Size: 54 x 35 mm

8 902319 031930

Manufactured by: / Fabriqué par:
Emcure
PHARMACEUTICALS LTD.
Hinjawadi, Pune [illegible] India.
TM Trade Mark Owners

Ver.6
201118

Product Name	INBEC Tablets (Non Royalty)	Sap code :	5100084590002	Reference Artwork	5100084590001
Packaging Material	Carton Artwork	Reason of change :	Editorial changes	Proof 1	20.11.2018
Size : Foil Width	-----	Country :	General Export		
Size : Foil Repeat Length	-----	Pack Size :	30 Tab		
Size : Strip Size	-----	Barcode No. :	8902319031930		
Size : Carton/Label	L. 52 x W. 54 x H. 98 mm	Pharmacode :	2709		
Size : PI - Open Size PI - Close Size	-----	No. of colours :	3		
PM Style/Type :	Reverse Tuck In Top Open	Min. Font Size :	5.2 Pt.		
Remark (If any) :	-----			Developed For :	Emcure – Hinjawadi Ms. Ishwaja Dalvi

PANTONE [illegible] C | PANTONE [illegible] C | Black