THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR BESICOR 2.5 (BISOPROLOL 2.5 MG) FILM COATED TABLETS

Version number 1.0
21 August, 2023

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1. Introduction

BESICOR 2.5 Tablets contains Bisoprolol fumarate as the active substance. Bisoprolol is a highly beta1-selective-adrenoceptor blocking agent, lacking intrinsic stimulating and relevant membrane stabilising activity. It only shows low affinity to the beta2-receptor of the smooth muscles of bronchi and vessels as well as to the beta2-receptors concerned with metabolic regulation. Therefore, bisoprolol is generally not to be expected to influence the airway resistance and beta2- mediated metabolic effects. Its beta1-selectivity extends beyond the therapeutic dose range. BESICOR 2.5 Tablets is approved in Tanzania for use in adults only.

Product details

Registration number	TAN 23 HM 0289
Brand name	BESICOR 2.5
Generic name, strength, and form	Each film coated tablet contains: Bisoprolol Fumarate 5mg
ATC classification	C07BB07- Bisoprolol and Thiazide
Distribution category	POM
Country of origin	India
Associated product	BESICOR 5 and BESICOR 10
Marketing Authorization Holder	Ajanta Pharma Limited Ajanta House, Charkop, Kandivli (W), Mumbai 400067, India
Local Technical Representative	Astra Pharma (T) Ltd, Plot No. 12, Vinginguti Industrial Area, Nyerere Road, Opp: Pepsi Tanzania Ltd, Dar Es Salaam,

1.1 Assessment procedure

The application for registration of BESICOR 2.5 Tablets was submitted on DD/MM/YYYY. The product underwent full assessment. Assessment was completed in 4 (four) rounds of evaluation and the product was registered on 01/06/2023.

1.2 Information for users

Visual description of the finished product	White to off white, circular, biconvex, film coated tablets with break line on one side and plain on other side
Primary packing material	Alu/Alu, Alu/PVC/Alu Blister
Secondary packing materials	Printed carton box
Shelf-life and storage condition	24 months, Do not store above 30°C.
Route of administration	Oral

Therapeutic indications	Treatment of Hypertension Treatment of stable chronic angina Treatment of stable chronic heart failure with reduced systolic left ventricular function in addition to ACE inhibitors, and diuretics, and optionally cardiac glycosides.

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: BESICOR 2.5

Composition: Each film coated tablet contains: Bisoprolol Fumarate 5mg

Pack size: 30's tablets

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

Storage conditions: Do not store above 30°C.

Manufacturer address: physical address of release site

Unique identifier: Not applicable

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

The details of the primary pack include:

Brand name and strength: BESICOR 2.5

Manufacturing details: batch number, manufacturing date and expiry date

Name of manufacturer: Ajanta Pharma 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 API was submitted in form of DMF.

General Information

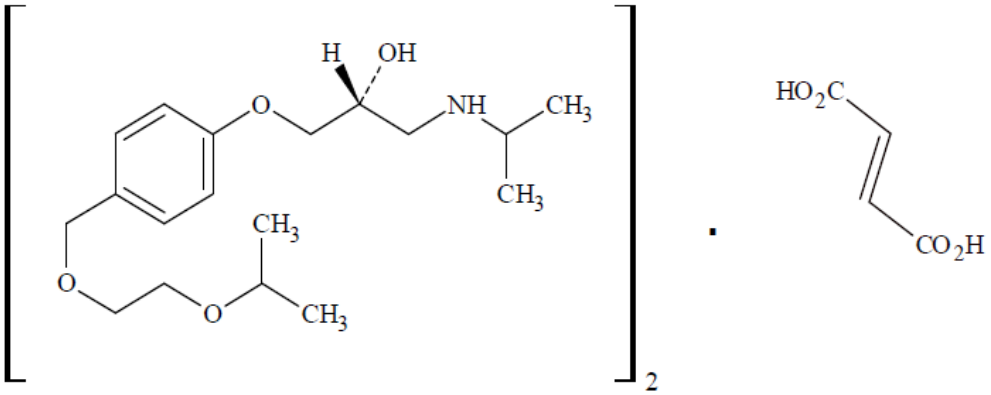
Bisoprolol Fumarate API is compendia in USP, Ph.Eur., and BP.

Molecular formula: $(C_{18}\ H_{31}NO_4)_2 \cdot C_4H_4O_4$

Chemical name:

- (2RS)-1-[4-[[2-(1-Methylethoxy) ethoxy] methyl] Phenoxy]-3-[(1-methylethyl) amino] propan-2-ol fumarate
- 2-Propanol,1-[4-[[2-(1-methylethoxy) ethoxy] methyl] Phenoxy]-3-[(1methylethyl) amino]-,(±)-,(E)-2- butenedioate (2:1) (salt)
- (±)-1-[[α-(2-Isopropoxyethoxy)-p-tolyl] oxy]-3-(isopropylamino)-2-propanol fumarate (2:1) (salt

Structure:



General properties

Bisoprolol Fumarate is white or almost white, slightly hygroscopic powder. It is freely soluble in methanol and very soluble in water. Bisoprolol Fumarate exhibits polymorphism and stable polymorph was produced throughout as confirmed by the XPRD and DSC techniques.

Bisoprolol Fumarate is BSC Class I characterized by high solubility and high permeability therefore its performance is unlikely to be affected by both PSD and polymorphism. Bisoprolol is used as a racemic mixture of R and S enantiomers.

Manufacture

Bisoprolol Fumarate API manufacturer is Mangalam Drugs and Organics Ltd, Unit-2, Plot No. 1203, G.I.D.C., Vapi, 396 195 Gujarat, India. The manufacturing complies with GMP requirements as evidenced by the GMP certificate issued by the Food and Drugs Control Administration, Gandhinagar. Bisoprolol Fumarate 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

Specifications

The API specifications were set as per Ph. Eur standards and ICHQ3A. The parameters monitored during quality control are: description, solubility, identification (IR), assay (HPLC), related compounds (HPLC), water determination (KF), sulphated ash, particle size, residual solvents (GC). Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The shelf-life period of Bisoprolol Fumarate API is 36 months when packed in colourless virgin / food grade single polyethylene bag (LDPE) and stored in airtight, light-resistant container. Store at controlled room temperature.

Quality of the Finished Pharmaceutical Product

Formulation

BESICOR 2.5 is a white to off white, circular, biconvex, film coated tablets with break line on one side and plain on other side

BESICOR 2.5 contains the Bisoprolol Fumarate and other ingredients listed here after: silicified microcrystslline cellulose, crospovidone, magnesium stearate, instacoat universal A05R03281 white, 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 manufacturer is Ajanta Pharma Ltd, Mirza-Palashbari Road, Village: Kokjhar, Dist: Kampur, Assam-781128, India. The compliance of the sites to TMDA GMP standards was confirmed through site inspection on 2– 3/5/2019.

Specifications

The FPP is 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 API (HPLC, TLC) and the colorant, average weight, water content (KF), uniformity of dosage units (by weight variation), dissolution (HPLC detection),

degradation products (HPLC), assay (HPLC), 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 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 original container with storage condition 'Do not store above 30°C'.

Safety and efficacy information

The biowaiver was approved based on additional strength.

BESICOR 2.5 fulfilled the criteria for waiving an in-vivo bioequivalence study as per relevant TMDA guidance. Dissolution profiles of BESICOR 2.5 (Bisoprolol Fumarate 5mg)) tablets was compared to BESICOR 10 (Bisoprolol Fumarate 10 mg)) tablets. Less than 85% of the labelled amount of Bisoprolol Fumarate had dissolved after 15 minutes in some media. As less in some media less than 85% is dissolved within 15 minutes. 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. BESICOR 2.5 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

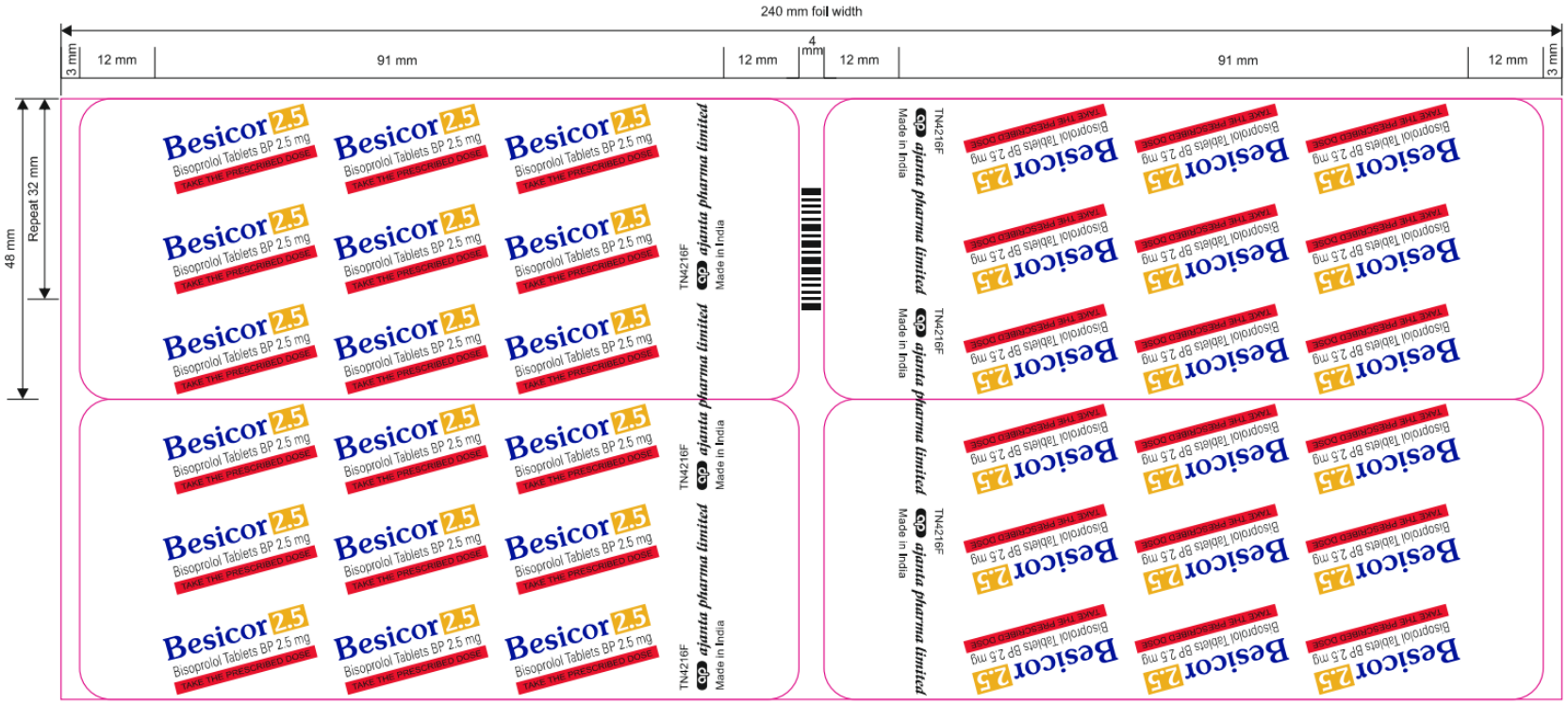
Application for renewal of registration was submitted on <DDMMYYYY>. The application was finalized in <number> rounds of evaluation. The product was confirmed to still be compliant to the standards of quality, safety and efficacy, hence registration was renewed on <DDMMYYYY>.

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:

Effective date: 03/10/2022