THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR ALIMAX 80 (TELMISARTAN 80MG) TABLETS

Version number 1.0
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TMDA Headquarters, Plot No. 56/1, Block E, Kisasa B Centre, Hombolo Road, P. O. Box 1253, Dodoma – Tanzania, Telephone: +255 (26) 2961989/2061990/+255 (22) 2450512/2450751/2452108, Email: info@tmda.og.tz, Website: **www.tmda.go.tz**

Toll free: 0800110084

1. Introduction

ALIMAX 80 mg tablets is a generic medicinal product containing the active substance Telmisartan.The originator product is “Micardis 80 mg tablets” by Boehringer Ingelheim International GmbH. Telmisartan is an orally active and specific angiotensin II receptor (type AT1) antagonist. Telmisartan displaces angiotensin II with very high affinity from its binding site at the AT1 receptor subtype, which is responsible for the known actions of angiotensin II. Telmisartan does not exhibit any partial agonist activity at the AT1 receptor. Telmisartan selectively binds the AT1 receptor. The binding is long-lasting. Telmisartan does not show affinity for other receptors, including AT2 and other less characterised AT receptors. The functional role of these receptors is not known, nor is the effect of their possible overstimulation by angiotensin II, whose levels are increased by telmisartan. Plasma aldosterone levels are decreased by telmisartan. Telmisartan does not inhibit human plasma renin or block ion channels. Telmisartan does not inhibit angiotensin converting enzyme (kininase II), the enzyme which also degrades bradykinin. Therefore, it is not expected to potentiate bradykinin-mediated adverse effects. ALIMAX 80 mg tablets is approved in Tanzania for use in adults and children (≥3 years).

Product details

Registration number	TAN 23 HM 0282
Brand name	ALIMAX 80
Generic name, strength, and form	Each tablet contains Telmisartan 80mg
ATC classification	Pharmacotherapeutic Group: Angiotensin II Antagonists, plain, ATC Code: C09CA07
Distribution category	POM
Country of origin	India
Associated product	ALIMAX 40
Marketing Authorization Holder	Delorbis Pharmaceuticals Ltd. 17, Athinon Street, Ergates Industrial Area, 2643 Ergates, P.O.BOX 28629, 2081 Lefkosia Cyprus
Local Technical Representative	Abacus Pharma (Africa) Ltd P.O.BOX 12294, Dar es Salaam

1.1 Assessment procedure

The application for registration of ALIMAX 80 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, oblong tablet, with a break line on one side
Primary packing material	oPA/AL/PVC-Aluminium blisters
Secondary packing materials	Printed carton box

Shelf-life and storage condition	36 months, Do not store above 30 °C.
Route of administration	Oral
Therapeutic indications	Hypertension Treatment of essential hypertension in adults. Cardiovascular prevention Reduction of cardiovascular morbidity in adults with: •Manifest atherothrombotic cardiovascular disease (history of coronary heart disease, stroke, or peripheral arterial disease) or •Type 2 diabetes mellitus with documented target organ damage.

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: ALIMAX 80

Composition: Each tablet contains Telmisartan 80mg

Pack size: 28 tablets

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

Storage conditions: Do not above 30°C

Manufacturer address: physical address of release site

Unique identifier: Not applicable

Special warnings/precautions or instructions for use: Not applicable

The details of the primary pack include:

Brand name and strength: ALIMAX 80

Manufacturing details: batch number, manufacturing date and expiry date

Name of manufacturer: Delorbis Pharmaceuticals Ltd

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

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

General Information

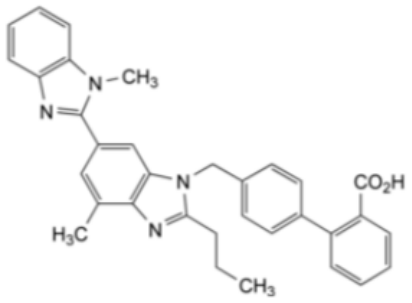
Telmisartan API is compendia in Ph.Eur., BP, USP.

Molecular formula: $C_{33}H_{30}N_4O_2$

Chemical name:

4′-[[4-Methyl-6-(1-methyl-1H-benzimidazol-2-yl)-2-propyl-1H-benzimidazol-1-yl] methyl] [1,1′-biphenyl]-2- carboxylic acid

Structure:



General properties

Telmisartan is a white or slightly yellowish crystalline powder, which practically is insoluble in water, slightly soluble in methanol, sparingly soluble in methylene chloride. It dissolves in 1 M sodium hydroxide. It exhibits polymorphism. Differential scanning calorimetry studies confirm that the manufacturing process used consistently produces the same polymorphic form**.**

Despite Telmisartan being classified as a BCS class II molecule, which is a poorly soluble API according to BCS, neither polymorphism nor particle size and distribution can be considered critical, as the API fully dissolves under the influence of sodium hydroxide during FPP manufacturing.

Manufacture

Telmisartan API manufacturer is Zhejiang Huahai Pharmaceutical Co., Ltd (Site I: Xunqio, China-317024 Linhai, Zhejiang Province, China. Site II: Chuannan, Duqiao, Linhai, Zhejiang 317016, China). The manufacturing complies with GMP requirements as evidenced by the GMP certificates issued by the Zhejiang Food and Drug Administration, China. Telmisartan 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 Ph. Eur standards and ICHQ3A. The parameters monitored during quality control are: Description, appearance of solution, identity by IR, sulphated ash, related substances, loss on drying, pH, assay, and NDMA and NDEA, residual solvent (GC). Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Telmisartan API is 36 months when packed in original container with storage condition 'Store below 25 ^{o}C'.

Quality of the Finished Pharmaceutical Product

Formulation

ALIMAX 80 is a white to off-white, oblong tablet, with a break line on one side

ALIMAX 80 contains the Telmisartan and other ingredients listed here after: sodium hydroxide, povidone, mannitol, maize starch, carmellosee calcium, purified water, sodium stearyl fumarate, magnesium stearate. 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 Zhejiang Huahai Pharmaceutical Co., Ltd, Xunqiao, Linhai, 317 024, Zhejiang province; Chuannan, Duqiao, Linhai, 317 016, Zhejiang Province, China; Delorbis Pharmaceuticals Ltd, 17, Athinon Street, Ergates Industrial Area, 2643 Ergates,

P.O.BOX 28629, 2081 Lefkosia, Cyprus. The compliance of the sites to TMDA GMP standards was confirmed through site inspection on DD/MM/YYYY.

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 by UV and HPLC, average weight, weight variation, uniformity of dosage units by content uniformity, dissolution, assay, related substances, and microbial contamination. 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 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 oPA/AL/PVC-Aluminium blisters with storage condition 'Do not store above 30 ^{o}C'

Safety and efficacy information

Safety and efficacy of ALIMAX 80 was established through a bioequivalence trial.

BE trial report number CTB09002 was submitted.

Study title	Evaluation of the bioequivalence of two oral preparations containing 80 mg telmisartan (Telmisartan Tablets 80 mg, Zhejiang Huahai Pharmaceutical Co., Ltd., China vs. Micardis® 80 mg Tabletten, Boehringer Ingelheim International GmbH, Germany). A monocentric, open, randomized, single dose, four-period, replicate crossover trial in healthy volunteers under fasting conditions
Study design	Open label, balanced, randomised, two-treatment, four-period, two-sequence, single-dose, replicate crossover bioequivalence study in healthy, adult, human subjects, under fasting condition
Study site	Clinical study site Erciyes University School of Medicine Hakan Cetinsaya GCP Clinical Research Center Talas Street 38039 Kayseri, Turkey Bioanalytical study site Anapharm Europe S.L. Encuny 22, 2a 08038 Barcelona, Spain

<table>
<tr><td>Study dates</td><td colspan="2"><table>
<tr><th>Activities</th><th>Dates</th></tr>
<tr><td>Period I (dosing)</td><td>04/06/2010</td></tr>
<tr><td>Period II (dosing)</td><td>11/06/2010</td></tr>
<tr><td>Period III (dosing)</td><td>18/06/2010</td></tr>
<tr><td>Period IV (dosing)</td><td>25/06/2010</td></tr>
<tr><td>Analysis (start date)</td><td>03/08/2010</td></tr>
<tr><td>Analysis (completion date)</td><td>18/08/2010</td></tr>
</table></td></tr>
<tr><td>Primary objective</td><td colspan="2">To investigate the bioequivalence of test product relative to reference product after a single oral dose administration of Telmisartan to healthy adults under fasting conditions</td></tr>
<tr><td>Secondary objective</td><td colspan="2">To monitor the safety and tolerability of a single dose of Telmisartan tablets when administered in 56 healthy adult human subjects under fasting condition</td></tr>
<tr><td>Number of participants</td><td colspan="2">Planned-32 subjects
Enrolled-32 subjects
Dosed-32 subjects
Withdrawn - 02 subject
Bio-sample analyzed -32 subjects
Pharmacokinetic and statistical data analyzed – 30 subjects</td></tr>
<tr><td>Monitored parameters</td><td colspan="2">Tmax, Cmax, AUC0→t, AUC0→∞, AUC% Extrapolation Kel and T1/2</td></tr>
<tr><td rowspan="2">Investigational medicinal products</td><td>Test Product</td><td>Reference product</td></tr>
<tr><td>Strength: 80 mg
Batch number: 140A10003
Expiry date: 09/2010</td><td>Strength: 80 mg
Batch number: 901216
Expiry date: 01/2013</td></tr>
<tr><td>Analytical method</td><td colspan="2">High Pressure Liquid chromatography – MS/MS – detector (LC-MS/MS) method was used for the determination of plasma concentrations of analyte</td></tr>
<tr><td>Statistical method</td><td colspan="2">SAS® PROC MIXED (SAS Institute Inc., USA) procedure</td></tr>
</table>

Efficacy results are summarized as follows:

Parameter	Test	Reference	% Ratio of geometric means	90 % Confidence interval	DF	CV (%)
AUC0-t (units)						
AUC0-inf (units)						
Cmax (units)						

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, Telmisartan Tablets 80 mg, Zhejiang Huahai Pharmaceutical Co., Ltd., China is equivalent and interchangeable with icardis® 80 mg Tabletten, Boehringer Ingelheim International GmbH, Germany 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. ALIMAX 80 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