THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR GLIMERON 1 (GLIMEPIRIDE 1 MG) TABLETS

Version number 1.0
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1. Introduction

Glimeron 1 tablets is a generic medicinal product containing the active substance Glimepiride.The originator product is “Amaryl 1 mg tablets” by Sanofi-Aventis. Glimepiride acts mainly by stimulating insulin release from pancreatic beta cells. As with other sulphonylureas this effect is based on an increase of responsiveness of the pancreatic beta cells to the physiological glucose stimulus. In addition, glimepiride seems to have pronounced extrapancreatic effects also postulated for other sulphonylureas. Glimeron 1 tablets is approved in Tanzania for use in adults and children (≥8 years).

Product details

Registration number	TAN 23 HM 0293
Brand name	Glimeron 1
Generic name, strength, and form	Each uncoated tablet contains Glimepiride 4 mg
ATC classification	A10BB12: Lowers blood glucose level
Distribution category	POM
Country of origin	India
Associated product	Glimeron 2, Glimeron 3, Glimeron 4
Marketing Authorization Holder	Ajanta Pharma Limited Ajanta House, Charkop, Kandivli (W), Mumbai 400067, India
Local Technical Representative	Astra Pharma (T) Ltd Dar es Salaam

1.1 Assessment procedure

The application for registration of Glimeron 1 was submitted on 15/01/2022. The product underwent full assessment. Assessment was completed in 7 (seven) rounds of evaluation and the product was registered on 01/06/2023.

1.2 Information for users

Visual description of the finished product	Light pink coloured, capsule shaped, biconvex, uncoated tablets, with break line on one side and plain on other side
Primary packing material	Alu-Alu blister pack
Secondary packing materials	Printed carton box
Shelf-life and storage condition	24 months, Do not store above 30 ^{o}C. Protect from moisture and light
Route of administration	Oral
Therapeutic indications	Glimepiride is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus.

	Limitations of Use Glimepiride should not be used for the treatment of type 1 diabetes mellitus or diabetic ketoacidosis, as it would not be effective in these settings

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: Glimeron 1

Composition: Each uncoated tablet contains Glimepiride1 mg

Pack size: 30 tablets

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

Storage conditions: Do not store above 30 ^{o}C. Protect from moisture and light

Manufacturer address: physical address of release site

Unique identifier: Not applicable

Special warnings/precautions or instructions for use: Contains lactose

The details of the primary pack include:

Brand name and strength: Glimeron1

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 quality of the API was submitted in form of CEP.

General Information

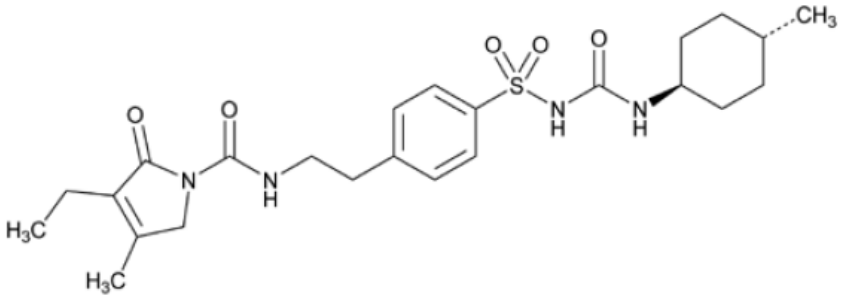
Glimepiride API is compendia in Ph.Eur., BP, USP.

Molecular formula: $C_{24}H_{34}N_4O_5S$

Chemical name:

1H -Pyrrole-1-carboxamide, 3-ethyl-2,5-dihydro-4-methyl-N-[2-[4-[[[[(4-methylcyclohexyl) amino] carbonyl] amino] sulfonyl] phenyl] ethyl]-2-oxo-, trans-.
1-[[p-[2-(3-Ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido) ethyl] phenyl] sulfonyl]-3-(trans-4-methylcyclohexyl) urea

Structure:



General properties

Glimepiride is a white or almost white powder. Glimepiride is practically insoluble in water, soluble in dimethylformamide, slightly soluble in methylene chloride, and very slightly soluble in methanol. Polymorphic form I is manufactured

Glimepiride is classified as a BCS class II molecule, which is a poorly soluble API according to BCS, therefore particle size and distribution is considered to be critical and test and limit for this parameter are included in the final API specifications.

Manufacture

Glimepiride API manufacturer is Glenmark Life Sciences Limited, Plot No 3109, GIDC Industrial Estate, Ankleshwar District Bharuch, Gujarat - 393 002 India. The manufacturing complies with GMP requirements as evidenced by the GMP certificates issued by the Food and Drugs Control Administration, Gujarat state, India. Glimepiride 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, solubility, identity by IR and HPLC, related substances, water, residue on ignition, limit of Cis-Isomer, assay, particle size, 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 Glimepiride API is 60 months when packed in polythene bag (clear), polythene bag (black), fiber board drum, HDPE drum with storage condition ‘Store in a tightly closed container at temperature not exceeding 25°C’.

Quality of the Finished Pharmaceutical Product

Formulation

Glimeron 1 is a light pink coloured, capsule shaped, biconvex, uncoated tablet, with break line on one side and plain on other side

Glimeron 1 contains the Glimepiride other ingredients listed here after: lactose (monohydrate), microcrystalline cellulose, sodium starch glycolate, povidone, polysorbate 80, ferric oxide, magnesium stearate 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. Ingredient, lactose is of safety concern therefore appropriate warnings were included in the product label.

Manufacture

The finished product manufacturers are Ajanta Pharma Limited,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 DD/MM/YYYY.

Specifications

The FPP is compendia. The manufacturer controls the quality of the finished product as per USP standards and ICH requirements. The parameters monitored during quality control are: Description, identification by HPLC and HPLC-UV, identity oof colourant, average weight, uniformity of weight, dimensions (length and width), hardness, friability, disintegration time, water content, dissolution, uniformity of dosage units by content uniformity, organic impurities, assay, and microbiological purity. 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 Alu-Alu blister pack with storage condition

Safety and efficacy information

Safety and efficacy of Glimeron 1 was established through <bioequivalence trial.

BE trial report number BIOS/2021/181 was submitted.

Study title	A randomized, open label, balanced, two treatments, two period, two sequence, two ways, cross-over, single oral dose, bioequivalence study of Glimepiride Tablets USP 1 mg of Ajanta Pharma Ltd. India with Amaryl® (Glimepiride Tablets) 1 mg manufactured by Sanofi-Aventis U.S. LLC, Bridgewater, NJ 08807 in healthy adult human male subjects under fasting conditions
Study design	A randomized, open label, balanced, two-treatment, two-period, two sequence, two ways, cross-over, single oral dose, bioequivalence study in healthy adult human male subjects under fasting conditions
Study site	Clinical Facility: Bio Scientific Research Laboratories (I) Pvt. Ltd. BIOS HOUSE, Plot No. 106/3, Aries Compound, Opp. Thakur Mall, S V Road, Mira Road, Thane 401104. Tel: +91-22- 28963582/ 28973512. Analytical Facility: Ajanta Bioanalytical Centre, Plot No. 29 C/D, Kandivali Industrial Estate, Charkop, Kandivali (W) Mumbai 400 067

<table>
<tr><td>Study dates</td><td colspan="2"><table>
<tr><th>Phase</th><th>Start Date</th><th>End Date</th></tr>
<tr><td>Clinical Period I</td><td>29/06/2022</td><td>02/07/2022</td></tr>
<tr><td>Clinical Period II</td><td>08/07/2022</td><td>11/07/2022</td></tr>
<tr><td>Bioanalysis</td><td>04/10/2022</td><td>14/10/2022</td></tr>
<tr><td>Statistical Analysis</td><td colspan="2">01/11/2022</td></tr>
</table></td></tr>
<tr><td>Primary objective</td><td colspan="2">To assess the bioequivalence of Glimepiride Tablets USP 1 mg of Ajanta Pharma Ltd. India with Amaryl® (Glimepiride Tablets) 1 mg manufactured by Sanofi-Aventis U.S. LLC, dose administration in adult human cancer patients under fasting conditions</td></tr>
<tr><td>Secondary objective</td><td colspan="2">To monitor the safety and tolerability of a single dose of Capecitabine tablets when administered</td></tr>
<tr><td>Number of participants</td><td colspan="2">Planned- 36 subjects
Enrolled- 36 subjects
Dosed- 36 subjects
Withdrawn - 00
Bio-sample analyzed – 36 subjects
Pharmacokinetic and statistical data analyzed – 36 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: 1 mg
Batch number: GT1941K
Expiry date:</td><td>Strength: 1 mg
Batch number: GT001
Expiry date:</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"></td></tr>
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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, Glimepiride Tablets USP 1 mg of Ajanta Pharma Ltd. India is equivalent and interchangeable with Amaryl® (Glimepiride Tablets) 1 mg manufactured by Sanofi-Aventis U.S. LLC 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. Glimeron 1 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: