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MINISTRYOFHEALTH

TANZANIAMEDICINES ANDMEDICALDEVICESAUTHORITY

PUBLIC ASSESSMENT REPORT FOR MG-2 (METFORMINHYDROCHLORIDE 500 MG AND GLIMEPIRIDE 2MG) TABLETS

Version number 01
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1. Introduction

MG-2 is a generic medicine of AMARYL (Glimepiride Tablets 2 mg) of Sanofi-Aventis U.S. LLC Bridgewater, NJ 08807 and GLUCOPHAGE (Metformin Hydrochloride 500 mg Tablets) of Bristol-Myers Squibb Company Princeton, NJ USA. MG-2 is an antidiabetic medicine belonging to A10B B12 (Blood glucose lowering drugs, excl. insulins: Sulfonamides, urea derivatives) group.

Glimepiride is an orally active hypoglycaemic substance belonging to the sulphonylurea group. Glimepiride acts mainly by stimulating insulin release from pancreatic beta cells. As with other sulfonylureas 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 sulfonylureas. Sulfonylureas regulate insulin secretion by closing the ATP-sensitive potassium channel in the beta cell membrane. Closing the potassium channel induces depolarisation of the beta cell and results -by opening of calcium channels - in an increased influx of calcium into the cell. This leads to insulin release through exocytosis. Glimepiride binds with a high exchange rate to a beta cell membrane protein which is associated with the ATP-sensitive potassium channel but which is different from the usual sulfonylureas binding site.

Metformin is a biguanide with antihyperglycaemic effects, lowering both basal and postprandial plasma glucose. It does not stimulate insulin secretion and therefore does not produce hypoglycaemic. Metformin may act via 3 mechanisms:

- reduction of hepatic glucose production by inhibiting gluconeogenesis and glycogenolysis
- in muscle, by increasing insulin sensitivity, improving peripheral glucose uptake and utilisation
- and delay of intestinal glucose absorption.

Metformin stimulates intracellular glycogen synthesis by acting on glycogen synthase. Metformin increases the transport capacity of all types of membrane glucose transporters (GLUT). In clinical studies, the major non glycemic effect of metformin is either weight stability or modest weight loss. In humans, independently of its action on glycaemia, immediate release metformin has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: immediate release metformin reduces total cholesterol, LDL cholesterol and triglyceride levels. A similar action has not been demonstrated with the prolonged release formulation, possibly due to the evening administration, and an increase in triglycerides may occur. MG-2 is approved in Tanzania for use in adults and elderly.

1.1 Product details

Registration number	TAN 21 HM 0289
Brand name	MG-2
Generic name, strength and	Glimepiride 2mg and Metformin Hydrochloride

form	500mg, Tablets
ATC classification	ATC code: A10B B12 Blood glucose lowering drugs, excl. insulins: Sulfonamides, urea derivatives
Distribution category	POM
Country of origin	India
Associated product	State any other product of formulation, strength or site that is linked or associated with the product if applicable
Marketing Authorization Holder	Resonant Pharmaceuticals Pvt. Ltd., A-904, Signature-2, Sharkhej Circle, Sharkhej Sanand Road, Ahmedabad-382210, Gujarat, INDIA
Local Technical Representative	Heko Pharmacy Limited, P.O. Box 2657, Plot No.32, Sikku Tandmati Street, DAR ES SALAAM.

1.2 Assessment procedure

The application for registration of MG-2 was submitted on 16th January, 2019. The product underwent full assessment. Assessment was completed in four rounds of evaluation. MG-2 was registered on 20th August, 2021

1.3 Information for users

Visual description of the finished product	Light yellow coloured, elongated, biconvex uncoated tablets, scored on one side
Primary packing material	Alu-Alu Blister
Secondary packing materials	Carton box
Shelf-life and storage condition	36 months Store below 30^0C, protected from light and moisture
Route of administration	Oral
Therapeutic indications	for the treatment of type 2 diabetes mellitus, when diet, physical exercise and weight reduction alone are not adequate

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 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: MG-2

Composition: Metformin, Glimepiride, Purified water, Gelatin, Corn Starch, Methylparaben, Propylparaben, Magnesium Stearate, Talc, Colloidal Silicon Dioxide, Croscarmellose Sodium and Quinoline Yellow Lake

Pack size: 5 x 10's

Manufacturing details: <batch number, manufacturing date, expiry date>

Storage conditions: Store below 30ºC, protected from light and moisture

Manufacturer address: East African (India) Overseas, Plot No. 1, pharmacity, Selaqui, Dehradun-248011, India.

Unique identifier: NA

Special warnings/precautions or instructions for use: <include warnings or IFU if applicable>

The details of the primary pack include:

Brand name and strength: MG-2 (Metformin 500 mg and Glimepiride 2 mg)

Manufacturing details: <batch number, manufacturing date, expiry date>

Name of manufacturer: East African (India) Overseas

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.

Describe any approved deviation to the requirements and the justification for the deviation.

Mock labels are <appended as annex I

3. Scientific discussion

Quality of Active Pharmaceutical Ingredient(s)

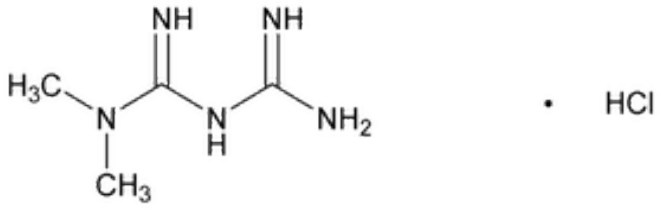
Information on quality of the API was submitted in form of Full details

General properties

Metformin Hydrochloride

Metformin Hydrochloride API is compendia in USP/BP Pharmacopeia
Molecular formula: $C_4H_{11}N_5.HCl$
Chemical name: 3-(diaminomethylidene)-1,1-dimethylguanidine; hydrochloride

Structure:



Metformin Hydrochloride is white crystals that is freely soluble in water; slightly soluble in alcohol practically insoluble in acetone and in methylene chloride. Metformin Hydrochloride is classified as BCS class III molecule which is highly soluble API according to BCS.

Manufacture

The API manufacturing site, Exemed Pharmaceuticals, Plot No. 133/1 & 133/2, GIDC, Selvas Road, Vapi-396 195, Taluka : Pardi , Valsad, Gujarat, India was noted to comply with WHO GMP requirements as evidenced by the GMP certificate issued by Food and Drugs Administration, Gujarat State, India. Metformin Hydrochloride 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, in-house standards and ICHQ3A. The parameters monitored during quality control are: Description, Solubility, Identification, Residue on Ignition, Organic Impurities, Loss on Drying, Assay and Residual Solvents

Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Metformin Hydrochloride API is 60 months when packed in Double polyethylene bags in Fibre Drum and stored at 25°C±2°C/ 65±5% RH.

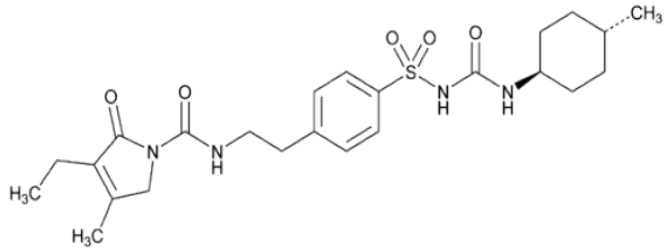
Glimepiride

Glimepiride API is compendia in USP/BP Pharmacopeia

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

Chemical name: 1- [[p-[2-(3 Ethyl-4-methyl-2-oxo-3-pyrroline1 carboxamido)ethyl]phenyl] sulfonyl]-3-(trans-4-methylcyclohexyl)urea;

Structure:



Glimepiride is White to almost white powder that is Soluble in Dimethyl formamide, slightly soluble in Methanol, sparingly soluble in Methylene Dichloride and practically insoluble in water. Glimepiride is classified as BCS class II molecule which is poorly soluble API according to BCS. Two polymorphic forms have been reported for Glimepiride. The X-ray diffraction (XRD) and Differential Scanning Calorimeter (DSC) data of API batches indicates that manufacturer; Indoco Remedies Ltd consistently produces crystalline Form I.

Manufacture

The API manufacturing site, Indoco Remedies Ltd., A-26, A-27, A-28/1 & A-28/2, MIDC Industrial Area, Patalganga,Village Kaire, Taluka Khalapur, District Raigad-410 220, India was noted to comply with WHO GMP requirements as evidenced by the GMP certificate issued by Food and Drugs Administration, Maharashtra State. 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 USP, in-house standards and ICHQ3A. The parameters monitored during quality control are: Description, Solubility, Identification, Residue on Ignition, Organic Impurities, Loss on Drying, Assay, Residual Solvents, Limit of cis-isomer (Glimepiride related compound A), particle size distribution and polymorphism (XRD). 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 Double polyethylene bags in Fibre Drum and stored at 25°C±2°C/ 65±5% RH.

Quality of the Finished Pharmaceutical Product

Formulation

MG-2 is a Light yellow coloured, elongated, biconvex uncoated tablet, plain on one side and has a score line on the other side. MG-2 contains Metformin Hydrochloride, Glimepiride and other ingredients listed here after Purified water, Gelatin, Corn Starch, Methylparaben, Propylparaben, Magnesium Stearate, Talc, Colloidal Silicon Dioxide, Croscarmellose Sodium and Quinoline Yellow Lake. The quantities of all ingredients are confirmed to be in line with the recommendations of Handbook of Pharmaceutical Excipients, Edition 8^{th} in terms of function and quantities. Methylparaben and Propylparaben are of safety concern therefore appropriate warnings were included in the product label.

Manufacture

The finished product was manufactured at Ease African (India) Overseas, 120, Suncity Business, Sector-54, Gurgaon- 122002, Haryana, INDIA. The compliance of the site to TMDA GMP standards was confirmed through site inspection on 27^{th} – 28^{th} June 2016

Specifications

The FPP is compendia USP/BP. The manufacturer controls the quality of the finished product as per BP, USP, in-house and ICHQ3B requirements. The parameters monitored during quality control are: Description, identification, average weight, dimension (length, thickness and width), hardness, uniformity of weight, uniformity of content, dissolution, related substances, microbial limit and assay. Compliance to the standard was established using batch analysis data and stability data.

Stability and container closure system

Stability studies were conducted on three batches of the finished product stored at 30°C ± 2°C, 75 % ± 5 % for 36 months and 40°C ± 2°C , 75 % ± 5 % for 6 months. Based on

the stability data presented, the approved shelf-life is 36 months when stored in Alu/Alu Blister at below 30°C.

Safety and efficacy information

Safety and efficacy of MG-2 was established through bioequivalence trial. BE trial/comparative dissolution report number HRL/GLM/342 Version number 00, Dated on 01/03/2016 was submitted.

In case of BE:

Study title	A balanced, open label, analyst blind, single center, two treatments, two period, two sequence, bioequivalence study of Glimepiride & Metformin Tablets 2mg/500mg of East African (I) Overseas, India with AMARYL (Glimepiride Tablets 2 mg) of Sanofi-Aventis U.S. LLC Bridgewater, NJ 08807 and GLUCOPHAGE (Metformin Hydrochloride 500 mg Tablets) of Bristol-Myers Squibb Company Princeton, NJ USA in 26 healthy, adult, male, human subjects under fasting conditions in a randomized, crossover design
Study design	A balanced, open label, analyst blind, single centre, two treatments, two period, two sequence, bioequivalence study in 26 healthy, adult, male, human subjects under fasting conditions.
Study site	Huclin Research Ltd No 4 Ticel Bio Park, Tharamani, Chennai - 600113
Study dates	Clinical Phase: Period I: 18th July 2016 to 20th July 2016 Period II: 25th July 2016 to 27th July 2016 Subject sample Analysis: Start Date: 02nd August 2016 End Date: 13th August 2016 Statistical Analysis Date: 29th August 2016
Primary objective	to assess the oral bioequivalence of Glimepiride & Metformin Tablets 2mg/500mg of East African (I) Overseas, India with AMARYL (Glimepiride Tablets 2 mg) of Sanofi-Aventis U.S. LLC Bridgewater, NJ 08807 and GLUCOPHAGE (Metformin Hydrochloride 500 mg Tablets) of Bristol-Myers Squibb Company Princeton, NJ USA in healthy, adult, male, human subjects under

	fasting conditions in a randomized, crossover design	
Secondary objective	To monitor the safety and tolerability of the test product as compared to the reference product in healthy, human subjects	
Number of participants	26 normal, healthy, adult, male	
Monitored parameters	AUC, Cmax, Tmax, T1/2, Kel	
Investigational medicinal products	Test Product	Reference product
	Strength: Glimepiride & Metformin Tablets 2mg/500mg Batch number: GMT-031601 Expiry date:	Strength: AMARYL (Glimepiride Tablets 2 mg) Batch number: OTO2241 Expiry date: 03/2017 Strength: GLUCOPHAGE (Metformin Hydrochloride 500 mg Tablets)) Batch number: X1532 Expiry date: 12/2016
Analytical method	LC-MS/MS	
Statistical method		

Efficacy results are summarized as follows:

Geometric Means and 90% Confidence Interval for Glimepiride (N=26)

Parameter	Test product (T)	Reference product (R)	Ratio (T/R) *100 %	90% CI	Intra CV (%)
lnCmax (ng/mL)	89.253	93.105	95.86	80.10 -11473	37.46
lnAUCt (ng/mL X hr)	818.611	902.554	90.70	81.30-101.19	22.34
lnAUCi (ng/mL X hr)	890.553	988.183	90.12	81.63-99.49	20.16

Geometric Means and 90% Confidence Interval for Metformin (N=26)

Parameter	Test product (T)	Reference product (R)	Ratio (T/R) *100 %	90% CI	Intra CV (%)
lnCmax (ng/mL)	688.986	661.639	104.13	90.59-119.71	28.68
lnAUCt (ng/mL X hr)	4916.850	4677.354	105.12	96.07-115.02	18.31
lnAUCi (ng/mL X hr)	5059.538	4824.311	104.88	96.03-114.54	17.92

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, MG-2 is equivalent and interchangeable with AMARYL (Glimepiride Tablets 2 mg) and GLUCOPHAGE (Metformin Hydrochloride 500 mg Tablets) under acceptable in vivo experimental conditions.

4. Benefit-Risk Assessment and Conclusion

On basis ofthe 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. MG-2 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 label