TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR MF-DAY ER 750 (METFORMIN HYDROCHLORIDE 750 MG) EXTENDED-RELEASE TABLETS

Version number 0.1,

March, 2022

P. O. Box 77150, EPI Mabibo, Off Mandela Road, Dar es Salaam, Tanzania
Tel: +255-22-2450512/2450751/ 2452108; Fax: +255-22-2450793
Email: info@tmda.go.tz; Website: mwww.tmda.go.tz

1. Introduction

MF-Day ER 750 is a generic medicine of metformin. MF-Day ER 750 is an antidiabetic medicine belonging to biguanides group. MF-Day ER 750 exerts is activity by decreasing hepatic glucose production, decreasing intestinal absorption of glucose, and improving insulin sensitivity by increasing peripheral glucose uptake and utilization. MF-Day ER 750 is approved in Tanzania for use in adults.

1.1 Product details

Registration number	TAN 21 HM 0153
Brand name	MF-Day ER 750
Generic name, strength and form	Metformin 750 mg extended-release tablets
ATC classification	A10BA02
Distribution category	POM
Country of origin	India
Associated product	MF-Day ER 500 and MF-Day 850
Marketing Authorization Holder	Aurobindo Pharma Limited Address: Plot No.2, Maitrivihar, Ameerpet, Hyderabad, Andhra Pradesh - 500 038, India.
Local Technical Representative	Generics and Specialties Limited, Plot No. 478 & 479, Zahara Towers, Mindu Street, Upanga, Dar es Salaam

1.2 Assessment procedure

The application for registration of MF-Day ER 750 was submitted on 20.02.2020. The product underwent full assessment. Assessment was completed in two (2) rounds of evaluation. MF-Day ER 750 was registered on 29/03/2021.

1.3 Information for users

Visual description of the finished product	White to off white, capsule shaped, beveled edge, biconvex uncoated tablets debossed with 'A' on one side and '19' on the other side.
Primary packing material	Clear PVC/Aclar – Plain Aluminium Blister pack, 3X10's
Secondary packing materials	Carton box
Shelf-life and storage condition	24 months, Store below 30°C.
Route of administration	Oral
Therapeutic indications	Treatment of type 2 diabetes mellitus in adults, particularly in overweight patients, when dietary management and exercise alone does not result is adequate glycaemic control. It may also be used as monotherapy or in combination with other oral antidiabetic agents or with insulin.

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: MF-Day ER 750
Composition: Each extended-release tablet contains: metformin hydrochloride 750 mg
Pack size: Clear PVC/Aclar – Plain Aluminium Blister pack, 3X10's in a carton box
Manufacturing details: batch number, manufacturing date, expiry date
Storage conditions: Do not store above 30^0C
Manufacturer address: Aurobindo Pharma Limited (Unit III), Survey No. 313 & 314, Bachupally, Bachupally Mandal, Medchal-Malkajgiri District, Telangana state, INDIA.
Unique identifier: barcode
Special warnings/precautions or instructions for use: keep out of reach of children

The details of the primary pack include:
Brand name and strength: MF-Day ER 750
Manufacturing details: batch number, manufacturing date, expiry date
Name of manufacturer: Aurobindo 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/currently not available>.

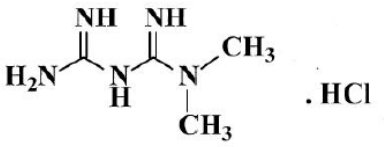
3. Scientific discussion

Quality of Active Pharmaceutical Ingredient(s)

Information on quality of the API was submitted in form of full details as per compendia requirements.

General properties
Metformin API is compendia in USP/BP.
Molecular formula: $C_4H_{11}N_5 \cdot HCl$
Chemical name: 1,1-Dimethylbiguanide hydrochloride

Structure:



Manufacture

The API manufacturing site, Aurobindo Pharma Limited, Unit - I, Survey No. 379, 385, 386, 388 to 396 Borpatla village, Hatnoora Mandal, Sangareddy District, Telangana, India was noted to comply with WHO GMP. Metformin API is manufactured by chemical synthesis using conventional/novel 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/BP standards and ICHQ3A. The parameters monitored during quality control are: description, identification, test for chloride, assay, residue on ignition, related substances, loss on drying, appearance of solution, 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 API is 48 months when packed in LDPE bag and stored at 25^0C.

Quality of the Finished Pharmaceutical Product

Formulation

MF-Day ER 750 is a white to off white, capsule shaped, beveled edge, biconvex uncoated tablets debossed with 'A' on one side and '19' on the other side packed in a clear PVC/Aclar – Plain Aluminium Blister pack of 3X10's then in a carton box. MF-Day ER 750 contains metformin and other ingredients listed here after < Microcrystalline Cellulose, Hypromellose, Hydroxy propyl Cellulose, Isopropyl alcohol, Purified water, Carbomer 941 and Magnesium Stearate. The quantities of all ingredients are confirmed to be in line with the recommendations of Handbook of Pharmaceutical Excipients, Edition 17 in terms of function and quantities.

Manufacture

The finished product was manufactured at Aurobindo Pharma Limited (Unit III), Survey No. 313 & 314, Bachupally, Bachupally Mandal, Medchal-Malkajgiri District, Telangana state, India. Zip Code: 500090. The compliance of the site to TMDA GMP standards was confirmed through site inspection on 22nd March, 2018.

Specifications

The FPP is USP. The manufacturer controls the quality of the finished product as per <reference monograph (USP) and ICHQ3B requirements. The parameters monitored during quality control are: description, identification, average weight, assay, dissolution, uniformity of dosage units, related substances, residual solvents and microbial limits. Compliance to the standard was established using batch analysis data and stability data.

Stability and container closure system

Stability studies were conducted on three (3) batches of the finished product stored at $30^{o}C \pm 2^{o}C/75\%RH \pm 5\%RH$ for 24 months and $40^{0}C \pm 2^{0}C/75\%RH \pm 5\%RH$ for three (3) months. Based on the stability data presented, the approved shelf-life is 24 months when stored in Alu/PVC blister pack at $30^{o}C$.

Safety and efficacy information

Safety and efficacy of MF-Day ER 750 was established through two bioequivalence trial.
First BE trial report number 143-10 was submitted.
In case of BE:

Study title	An open label, Randomized, Two treatment, Two sequence, Two Period, cross-Over, Single-Dose, Comparative Oral Bioavailability Study of Metformin Hydrochloride ER Tablets 750 mg (Test) of Aurobindo Pharma Limited, India and Glucophage XR tablets 750 mg (Metformin Hydrochloride ER Tablets 750 mg) (Reference) of Bristol-Myers Squibb company, USA. In 36 healthy, adult human subjects under fasting conditions.	
Study design	An open label, randomized, two-treatment, two-sequence, two-period, crossover, single dose bioavailability study in 36 healthy, adult, human subjects under fasting conditions.	
Study site	AXIS Clinicals Limited, Plot No: 33-35, Alluri Sitaramaraju Nagar, Opp. J.P.N. Nagar, Miyapur, Hyderabad-500 050, India	
Study dates	15th May 2010 - 05-06.2010	
Primary objective	To compare the rate and extent of absorption of Metformin Hydrochloride ER tablets 750 mg (Test) of Aurobindo Pharma Limited, India and Glucophage XR tablets 750 mg (Metformin Hydrochloride ER Tablets 750 mg) (Reference) of Bristol-Myers Squibb Company, USA when given in equal doses of single oral dose in healthy, adult human subjects.	
Secondary objective	To monitor the adverse events and to ensure the safety of the subjects.	
Number of participants	29	
Monitored parameters	Cmax, Tmax, AUC_{0-t} and AUC_{0-inf}	
Investigational medicinal products	Test Product	Reference product
	Strength: 750mg Batch number: MQ7510001 Expiry date: Feb 2012	Strength: 750 mg Batch number: 9C3001A Expiry date: Mar 2012
Analytical method	HPLC – UV detection method	
Statistical method	General Linear Model (PROC GLM) of SAS® version 9.1.3 software	

Efficacy results are summarized as follows:

Parameter	**Test**	**Reference**	**90 % Confidence interval**	**DF**	**CV (%)**

AUC0-t (units)	9808.19	10308.76	87.87-103.02	27	17.92
AUC0-inf (units)	10168.97	10712.17	87.79-102.64	27	17.60
Cmax (units)	915.23	891.65	94.54-111.44	27	18.54

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, MF-Day ER 750 is equivalent and interchangeable with comparator under acceptable in vivo experimental conditions.

Secondary BE trial report number 144-10 was submitted.
In case of BE:

Study title	An open label, Randomized, Two treatment, Two sequence, Two Period, cross-Over, Single-Dose, Comparative Oral Bioavailability Study of Metformin Hydrochloride ER Tablets 750 mg (Test) of Aurobindo Pharma Limited, India and Glucophage XR tablets 750 mg (Metformin Hydrochloride ER Tablets 750 mg) (Reference) of Bristol-Myers Squibb company, USA. In 36 healthy, adult human subjects under fed conditions	
Study design	An open label, randomized, two-treatment, two-sequence, two-period, crossover, single dose bioavailability study in 36 healthy, adult, human subjects under fasting conditions.	
Study site	AXIS Clinicals Limited, Plot No: 33-35, Alluri Sitaramaraju Nagar, Opp. J.P.N. Nagar, Miyapur, Hyderabad-500 050, India	
Study dates	15th May 2010 - 05-06.2010	
Primary objective	To compare the rate and extent of absorption of Metformin Hydrochloride ER tablets 750 mg (Test) of Aurobindo Pharma Limited, India and Glucophage XR tablets 750 mg (Metformin Hydrochloride ER Tablets 750 mg) (Reference) of Bristol-Myers Squibb Company, USA when given in equal doses of single oral dose in healthy, adult human subjects.	
Secondary objective	To monitor the adverse events and to ensure the safety of the subjects	
Number of participants	29	
Monitored parameters	Cmax, Tmax, AUC_{0-t} and AUC_{0-inf}	
Investigational medicinal products	Test Product	Reference product
	Strength: 750mg Batch number: MQ7510001 Expiry date: Feb 2012	Strength: 750 mg Batch number: 9C3001A Expiry date: Mar 2012
Analytical method	HPLC – UV detection method	
Statistical method	General Linear Model (PROC GLM) of SAS® version 9.1.3 software	

Efficacy results are summarized as follows:

Parameter	Test	Reference	90 % Confidence interval	DF	CV (%)
AUC0-t (units)	9870.55	9643.96	98.11-106.77	27	10.49
AUC0-inf (units)	10170.71	102.35	97.44-106.24	27	10.71
Cmax (units)	905.56	858.97	99.80-111.37	27	13.62

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, MF-Day ER 750 is equivalent and interchangeable with Glucophage XR tablets 750 mg 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. MF-Day ER 750 is recommended for registration.

5. Post-approval updates

Variation applications

Reference number	Date submitted	Change requested	Recommendation	Granting date
NA	NA	NA	NA	NA

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