THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR FAROGLIP SM 50/1000 (50MG SITAGLIPTIN (AS PHOSPHATE MONOHYDRATE) AND 1000MG METFORMIN (AS HYDROCHLORIDE) FILM COATED TABLETS

Version number 01
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1. Introduction

FAROGLIP SM 50/1000 is a generic medicine of Janumet 50mg/1g film coated tablets of Merck Sharp & Dohme Ltd, is a fixed dose combination containing 2 antihyperglycaemic agents with complementary mechanisms of action for lowering glucose has the potential to provide a new treatment option for patients with Type 2 diabetes mellitus (T2DM). FAROGLIP SM 50/1000 is approved in Tanzania for use only in adult patients.

1.1 Product details

Registration number	TAN 22 HM 0011
Brand name	FAROGLIP SM 50/1000
Generic name, strength, and form	Each film coated tablet contains: 50 mg Sitagliptin (as Sitagliptin Phosphate Monohydrate) 1000 mg Metformin (as Metformin Hydrochloride)
ATC classification	ATC code: A10BD07-Drugs used in diabetes, Combinations of oral blood glucose lowering drugs,
Distribution category	POM
Country of origin	Bangladesh
Associated product	N/A
Marketing Authorization Holder	Faromed Lifesciences LLP Plot No. 29-33, Ancillary Industrial Area, Deonar, Govandi, Mumbai-400 043, India. Email : info@faromed.at
Local Technical Representative	Planet Pharmaceutical Limited, House No. 23, Plot No. 20, Kipata/Nyamwezi Street Kariakoo,Dar es Salaam.

1.2 Assessment procedure

The application for registration of FAROGLIP SM 50/1000 was submitted on <DDMMYYYY>. The product underwent full assessment. Assessment was completed in 3 (three) rounds of evaluation and the product was registered on 10 January 2022.

1.3 Information for users

Visual description of the finished product	Deep brown, oval, biconvex film coated tablets, engraved with 'ACME' on one face and a breakline on the other face.
Primary packing material	Aluminium – PVC/PDVC Blister
Secondary packing materials	A printed carton box
Shelf-life and storage condition	24 months, Do not store above 30°C.Protect from light.
Route of administration	Oral
Therapeutic indications	For adult patients with type 2 diabetes mellitus: FAROGLIP SM 50/1000 is indicated as an adjunct to diet and exercise to improve glycaemic

	control in patients inadequately controlled on their maximal tolerated dose of metformin alone or those already being treated with the combination of sitagliptin and metformin. FAROGLIP SM 50/1000 is indicated in combination with a sulphonylurea (i.e., triple combination therapy) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a sulphonylurea. FAROGLIP SM 50/1000 is indicated as triple combination therapy with a peroxisome proliferator-activated receptor gamma (PPARγ) agonist (i.e., a thiazolidinedione) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a PPARγ agonist. FAROGLIP SM 50/1000 is also indicated as add-on to insulin (i.e., triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control in patients when stable dose of insulin and metformin alone do not provide adequate glycaemic control.

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: FAROGLIP SM 50/1000

Composition: Each film coated tablet contains: 50 mg Sitagliptin (as Sitagliptin Phosphate Monohydrate) and 1000 mg Metformin (as Metformin Hydrochloride)

Pack size:2x10 tablets

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

Storage conditions: Do not store above 30°C.Protect from light
Manufacturer address: physical address of release site

Unique identifier: Not applicable

Special warnings/precautions or instructions for use: Please see inner leaflet

The details of the primary pack include:

Brand name and strength: FAROGLIP SM 50/1000 (50 mg Sitagliptin (as Sitagliptin Phosphate Monohydrate) and 1000 mg Metformin (as Metformin Hydrochloride))

Manufacturing details: batch number, manufacturing date and expiry date

Name of manufacturer: The ACME Laboratories 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 APIs were submitted in form of DMFs.

Sitagliptin Phosphate Monohydrate:

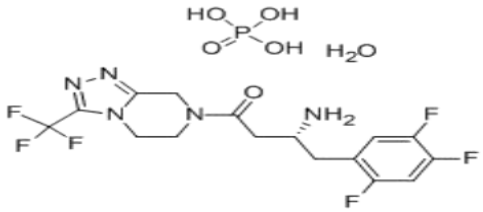
General Information

Sitagliptin Phosphate Monohydrate API is compendia in USP, Ph.Eur./BP.

Molecular formula: $C_{16}H_{20}F_6N_5O_6P$

Chemical name:
7-[(3R)-3-Amino-1-oxo-4-(2,4,5-trifluorophenyl)Butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyrazinephosphatemonohydrate or 1,2,4-Triazolo[4,3-a]pyrazine, 7-[(3R)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-, phosphate (1:1) monohydrate

Structure:



General properties

Sitagliptin is a white to off-white powder and exhibits pH dependent aqueous solubility. It is soluble in water and N, N-dimethyl formamide, slightly soluble in methanol, very slightly soluble in ethanol,
acetone and acetonotrile and insoluble in isopropanol and isopropyl acetate. The above-mentioned active substance contains a chiral centre and is used as a single enantiomer (R). Enantiomeric purity is controlled routinely by suitable analytical methods.

According to Biopharmaceutics Classification System (BCS), Sitagliptin is classified as Class 1 compound (high solubility, high permeability) so neither polymorphism nor particle size distribution can affect the quality or performance of the finished product.

Manufacture

Sitagliptin Phosphate Monohydrate API manufacturer is Anqing World Chemical Co. Ltd, No.21 Huancheng West Road, Anqing County, Anhui Province, China. The manufacturing complies with GMP requirements as evidenced by the GMP certificate issued by the <state the issuing authority>. Sitagliptin Phosphate Monohydrate 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 standards and ICHQ3A. The parameters monitored during quality control are: Appearance, Identification (IR, HPLC and Phosphate test), Water content, Related substances (HPLC), Assay (By HPLC), Enantiomeric purity, and Residual solvents (GC). Compliance to these specifications were established via batch analysis data and stability studies.

<u>Stability and container closure system</u>

The re-test period of Sitagliptin Phosphate Monohydrate API is 36 months when packed in Double layer polyethylene bags with storage condition ‘Store below 25 °C’.

Metformin Hydrochloride:

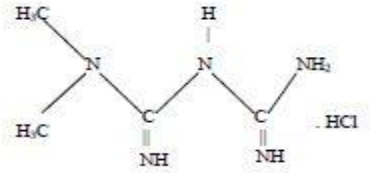
General Information

Metformin Hydrochloride API is compendia in USP, Ph.Eur./BP.

Molecular formula: $C_4H_{11}N_5$. HCl

Chemical name:
1, 1 – Dimethylbiguanide Hydrochloride N, N-Dimethylimidodicarbonimidicdiamide N'-Dimethylguanyl guanidine or Imidodicarbonimidic diamide.

Structure:



General properties

Metformin Hydrochloride is a white, hygroscopic crystalline powder that is odourless and has a bitter taste. The compound is freely soluble in water, slightly soluble in ethanol and practically insoluble in chloroform, acetone, ether and in ethylene chloride. Metformin Hydrochloride manufactured by proposed manufacturer conforms to Polymorph - II based on the description from the published literature. According to Biopharmaceutics Classification System (BCS), Metformin Hydrochloride is classified as Class 3 compound (high solubility, low permeability) so neither polymorphism nor particle size distribution can affect the quality or performance of the finished product.

Manufacture

Metformin Hydrochloride API manufacturers are Wanbury Limited, Doctors Organic Chemical Division K Illindalaparru- 534217, Iragavaram Mandal, West Godavari District Andhra Pradesh; India and Wanbury Limited, A-15, M.I.D.C. Industrial Area, Patalganga, Dist-Raigad-410 220, Maharashtra, India. The manufacturing complies with GMP requirements as evidenced by the GMP certificate issued by the Drugs Control Administration of Andhra Pradesh and Food & Drugs Administration M.S. 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 BP/Ph.Eur. standards and ICHQ3A. The parameters monitored during quality control are: Appearance, Solubility, Identification (IR, Melting point,

TLC, Color test, and Chloride), Appearance of solution, Loss of drying, Sulphated ash, Related substances (HPLC), Assay (By HPLC), 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 Metformin Hydrochloride API is 60 months when packed in Double layer polyethylene bags.

Quality of the Finished Pharmaceutical Product

Formulation

FAROGLIP SM 50/1000 is a Deep brown, oval, biconvex film coated tablets, engraved with 'ACME' on one face and a breakline on the other face.

FAROGLIP SM 50/1000 contains the Sitagliptin Phosphate Monohydrate and Metformin hydrochloride and other ingredients listed here after: Microcrystalline cellulose, Hypromellose, Povidone, Croscarmellose Sodium, Magnesium Stearate, Instamoistshield Aqua – II ((Polyvinyl Alcohol, Polyethylene Glycol, Talc, Triacetin, Tribasic Calcium Phosphate, and Titanium Dioxide), Opadry OY-B-37203 (Polyvinyl Alcohol, Titanium Dioxide, Talc, Red iron oxide, Yellow iron oxide, Lecithin (soy), Xanthan gum, and Black iron oxide). 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 The ACME Laboratories Ltd, Dhulivita, Dhamrai, Dhaka, Bangladesh. The compliance of the site to TMDA GMP standards was confirmed through site inspection on 21st June 2021.

Specifications

The FPP is non-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: Appearance (By visual), identification (By HPLC and HPLC-UV spectrum), Loss on drying, Average weight, Uniformity of weight, Disintegration, Uniformity of dosage units, Dissolution (By HPLC), Related substances (HPLC), Assay (HPLC), Residual solvent (GC), Microbial enumeration tests, and Test for specified Microorganisms. Compliance to the standard was established using batch analysis data and stability data.

Stability and container closure system

Stability studies were conducted on a 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 Aluminium–PVC/PDVC blister with storage condition 'Do not store above 30°C.Protect from light'.

Safety and efficacy information

Safety and efficacy of FAROGLIP SM 50/1000 was established through a bioequivalence trial.

BE trial report number 03/16/341 was submitted.

Study title	A randomized, open-label, balanced, two-treatment, two-period, two-sequence, single-dose, crossover, comparative, oral bioavailability study of Sitamin 1000 Film Coated Tablet containing Sitagliptin Phosphate 50mg + Metformin HCl 1000 mg manufactured by The ACME Laboratories Limited, Dhulivita, Dhamrai Dhaka, Bangladesh with marketed samples of Janumet 50 mg/1 gm Film Coated Tablet (Containing Sitagliptin Phosphate 50 mg + Metformin HCl 1 gm) manufactured by Patheon Puerto Rico Inc., USA, in 24 healthy adult, human, male subjects under fasting conditions.	
Study design	A randomized, open-label, balanced, two-treatment, two-period, two-sequence, single-dose, crossover oral bioequivalence study in normal healthy adult human subjects under fasting conditions.	
Study site	TAAB Biostudy Services 69, Ibrahim Road, 1st Floor, Flat No.: 1A, Jadavpur, Kolkata-700032 Email: tab_bio@yahoo.com	
Study dates	21 August, 2016-21 September, 2016	
Primary objective	To assess whether the test product is bioequivalent to reference product	
Secondary objective	Assessment of safety and tolerability of the subjects.	
Number of participants	Planned for inclusion: 24 Subjects Enrolled: 24 Total number of subjects completed the study: 24 Drop-out / withdrawn: 00 Included subjects in statistical analysis: 24	
Monitored parameters	Tmax, Cmax, AUC0→t, AUC0→∞, AUC% Extrapolation Kel and T1/2	
Investigational medicinal products	Test Product	Reference product
	Strength: 50 mg/1000 mg Batch number: T2396005 Expiry date: March 2018	Strength: 50 mg/1000 mg Batch number: L004429 Expiry date: November 2017
Analytical method	Analysis of plasma concentrations of Sitagliptin and Metformin were done by a validated Liquid Chromatography method with tandem mass spectrometry	
Statistical method	WinNonlin version 5.3.	

Efficacy results are summarized as follows:

Sitagliptin:

Parameter	Reference	Test	95 % Confidence interval	DF	CV (%)
Cmax (ng/mL)	137.01	125.84	98.79-100.57	22	12.859
AUC0-t (hr.ng/mL)	705.73	684.25	99.55-100.98	22	12.859
AUC0-inf (ng.hr/mL)	807.01	774.07	99.26-100.83	22	14.285

Metformin:

Parameter	Reference	Test	95 % Confidence interval	DF	CV (%)
Cmax (ng/mL)	2039.85	1961.48	98.60-100.76	22	12.859
AUC0-t (hr.ng/mL)	11789.74	11923.65	99.41-101.73	22	12.859
AUC0-inf (ng.hr/mL)	12209.14	12320.47	99.10-100.99	22	14.285

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, Sitamin 1000 Film Coated Tablet containing Sitagliptin Phosphate 50mg + Metformin HCl 1000 mg manufactured by The ACME Laboratories Limited is equivalent and interchangeable with Janumet 50 mg/1 gm Film Coated Tablet (Containing Sitagliptin Phosphate 50 mg + Metformin HCl 1 gm) manufactured by Patheon Puerto Rico Inc. 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. FAROGLIP SM 50/1000 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

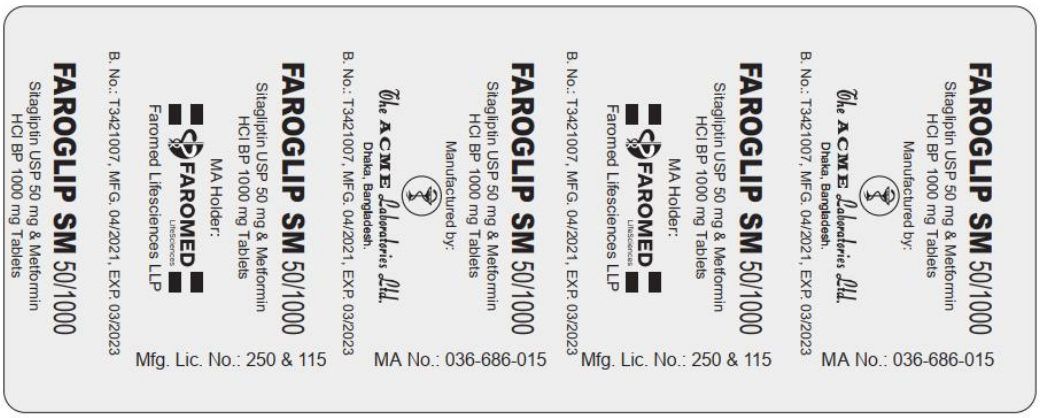
Application for renewal of registration was submitted on <DDMMYYYY>. The application was finalized in <number> rounds of evaluation. The product was confirmed to still be compliant to the standards of quality, safety and efficacy, hence registration was renewed on <DDMMYYYY>.

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