THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR SITAPRIL 100® (SITAGLIPTIN PHOSPHATE MONOHYDRATE EQUIVALENT TO SITAGLIPTIN 100 MG) FILM COATED TABLETS

Version number 01, 03/01/2023

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1. Introduction

Sitapril 100® is a s a generic medicine of Janumet ® (Sitagliptin Phosphate Monohydrate 100 mg) tablets, Merck Sharp & Dohme (UK) Limited. Sitapril 100® is an Anti-Diabetic medicine belonging to Dipeptidyl peptidase 4 (DPP-4) inhibitors group. Sitapril 100® exerts is activity by increasing the levels of the Incretin hormones Glucagon-like Peptide-1 (GLP- 1) and glucose-dependent insulinotropic polypeptide (GIP). Sitapril 100® is approved in Tanzania for use in adults only.

1.1 Product details

Registration number	TAN 21 HM 0399
Brand name	Sitapril 100®
Generic name, strength and form	Sitagliptin Phosphate Monohydrate 100 mg Film Coated Tablets
ATC classification	ATC Code-A10BH01 Anti-Diabetic, Dipeptidyl peptidase 4 (DPP-4) inhibitors
Distribution category	POM
Country of origin	India
Associated product	Sitapril 25® and Sitapril 50®
Marketing Authorization Holder	Ajanta Pharma Limited Address: Ajanta House, Charkop, Kandivli (W), Mumbai 400067, India
Local Technical Representative	Astra Pharma (T) Limited. Address: Plot no-12, Vingunguti Industrial Area, Nyerere Road, opp: Pepsi tanzania Ltd, Dar -Es- Salaam.

1.2 Assessment procedure

The application for registration of Sitapril 100® was submitted on 29/01/2021. The product underwent full assessment. Assessment was completed in 2(two) rounds of evaluation. Sitapril 100® was registered on 09/10/2021.

1.3 Information for users

Visual description of the finished product	Beige colored, round, film coated tablets debossed ‘ST3’ on one side and plain on other side
Primary packing material	Alu-Alu blister pack
Secondary packing materials	A printed carton box
Shelf-life and storage condition	24 months, Do not store above 30°C
Route of administration	Oral

Therapeutic indications	Sitagliptin is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

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 both full prescribing information as per SmPC and simplified information for patients.

Container labels

The product label information is presented in English. Details in the secondary pack label include:

Brand name: Sitapril 100®

Composition: Sitagliptin Phosphate Monohydrate equivalent to Sitagliptin 100 mg

Pack size: 30 tablets

Manufacturing details: batch number, manufacturing date, expiry date

Storage conditions: Do not store above 30°C

Manufacturer address: Ajanta Pharma Limited, B-4-5-6, MIDC Industrial Area, Paithan, Aurangabad, 431148, Dist: Aurangabad, Maharashtra, India.

Unique identifier: N/A

Special warnings/precautions or instructions for use: Read the patient information Leaflet carefully before use

The details of the primary pack include:

Brand name and strength: Sitapril 100®

Manufacturing details: batch number, manufacturing date, 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 Ingredient(s)

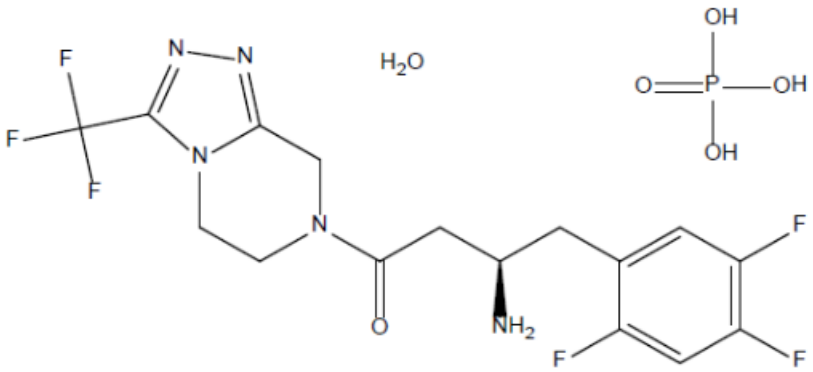
Information on quality of the API was submitted in form of Full details.

General properties
Sitagliptin Phosphate Monohydrate API is compendia in USP/BP.

Molecular formula: $C_{16}H_{15}F_6N_5OH_3PO_4H_2O$

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

Structure:



Critical physico-chemical properties are:

The active substance is White to off-white crystalline powder Soluble in water and N, N-Dimethyl formamide, slightly soluble in methanol and insoluble in2-propanol. It is not known to exhibit polymorphism or to form defined hydrates.

Manufacture
The API manufacturing site, MSN Pharmachem Private Limited, Plot No.: 212 / A,B,C,D, Phase-II, IDA Pashamylaram, Pashamylaram (Village), Patancheru (Mandal), Sangareddy District,Telangana, Pin code: 502 307, India was noted to comply with WHO GMP requirements as evidenced by the GMP certificate issued by Drugs Control Administration of Government of Telangana. 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: description (visual), solubility, identification (IR, HPLC, and Phosphates), assay (HPLC), related substances (HPLC), enantiomeric purity (HPLC), residual solvents (GC), water content (KF), solid state (XRPD), particle size distribution (laser diffraction), bulk density, phosphate content. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The shelf-life period of Sitagliptin Phosphate Monohydrate API is 60 months when packed in stored in the original packing material and stored at controlled room temperature between 20°C and 25°C (excursions allowed between 15°C and 30°C).

Quality of the Finished Pharmaceutical Product

Formulation

Sitapril 100® is a beige colored, round, film coated tablets debossed 'ST3' on one side and plain on other side.

Sitapril 100® contains Sitagliptin Phosphate Monohydrate and other ingredients listed here after: Microcrystalline Cellulose, Anhydrous Dibasic Calcium Phosphate, Croscarmellose Sodium, Magnesium Stearate, Sodium Stearyl Fumarate, Instacoat Aqua II A02G10251 Beige (Polyvinyl Alcohol, Polyethylene Glycol 3350, Talc, Titanium Dioxide, Yellow Iron Oxide and Red Iron Oxide), Purified water. 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.

Manufacture

The finished product was manufactured at Ajanta Pharma Limited, B-4-5-6, MIDC Industrial Area, Paithan, Aurangabad, 431148, Dist: Aurangabad, Maharashtra, India. The compliance of the site to TMDA GMP standards was confirmed through site inspection on DD/MM/YY.

Specifications

The FPP is BP/USP. The manufacturer controls the quality of the finished product as per USP standards and ICH requirements. The parameters monitored during quality control are: description (visual), identity of API (IR and HPLC), assay (HPLC), average weight, uniformity of dosage (weight variation), dissolution (HPLC), water (KF), disintegration, elementary impurities, 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 three (3) batches of the finished product stored at 30^0 ± 2°C & 75% ± 5% RH for 24 months and 40^0 ± 2°C & 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 at Do not store above 30°C.

Safety and efficacy information

Safety and efficacy of Sitapril 100® was established through bioequivalence trial.

BE trial report number ARL/17/425 was submitted.

In case of BE:

Study title	A study is a Randomized, Open Label, Balanced, Two Treatment, Two period, Two Sequence, Single Dose, Crossover Bioequivalence Study of Sitagliptin Tablets, USP 100 mg of Ajanta Pharma Ltd., India with Januvia® (sitagliptin) tablets 100 mg of Merck Sharp & Dohme Corp., in Normal, Healthy, Adult, Male and Female Human Subjects under Fasting Conditions.
Study design	Randomized, open label, balanced, two-treatment, two-period, two sequence, single dose, crossover design BE study in normal, healthy, adult, male human subjects under fasting conditions
Study sites	Clinical, Bio-Analytical and Statistical Facility: Accutest Research Laboratories (I) Pvt. Ltd. (Unit-II) Opposite The Grand Bhagwati Hotel, Sarkhej-Gandhinagar Highway, Bodakdev, Ahmedabad - 380059, India Clinical Laboratory Facility: SYMMERS PATH CARE 8, 9 Ground Floor Narayan Chambers, B/H Patang Hotel, NR. Nehrubridge, Ahmedabad 380009, Gujarat PH. 079-26578364 X-Ray Facility: Shachi X-Ray, Sonography & Colour Doppler Clinic F-2, 3 Balaji Center, Opposite Gurukul, Drive-in Road, Memnagar, Ahmedabad-380052, India Emergency Facility: SAL Hospital and Medical Institute Opp. Doordarshan, Drive in road, Ahmedabad – 380 052, Gujarat, India
Study dates	Clinical Phase: 15 November 2019 – 26 November 2019 Clinical Completion Date: 26 November 2019 Study Sample Analysis: 28 November 2019 – 09 December

	2019 Statistical Analysis Date: 17 December 2019	
Primary objective	To investigate the bioequivalence of Sitagliptin Tablets, USP 100 mg of Ajanta Pharma Ltd., India with Januvia® (sitagliptin) tablets 100 mg of Merck Sharp & Dohme Corp, following a single oral dose of test product or reference product administration under fasting conditions	
Secondary objective	To monitor the adverse events and to ensure the safety of the subjects	
Number of participants	A total of 24 subjects were dosed in Period-I and II. None of the subject was discontinued from the study. Hence, a total of 24 subjects completed the clinical phase successfully. The data of 24 subjects were analysed for PK and safety of the study products	
Monitored parameters	Tmax, Cmax, AUC0→t, AUC0→∞, AUC% Extrapolation Kel and T1/2	
Investigational medicinal products	Test Product	Reference product
	Strength: 100 mg Batch number: PA1049H Expiry date:07/2021	Strength: 100 mg Batch number: N025017 Expiry date: 17/08/2020
Analytical method	LC-MS/MS method was used for the determination of plasma concentration of analyte	
Statistical method	Statistical Analysis Software SAS® (SAS Institute Inc., USA) Version 9.2	

Efficacy results are summarized as follows:

Geometric Means, Ratios and 90% Confidence Intervals of Sitagliptin (N=24)

Parameters	*Geometric mean		% Ratio (T/R)	90 % Confidence Interval for T/R Ratio	
	Test (T)	Reference (R)		Lower Limit	Upper Limit
AUC_{0-inf}	4427.5091	4562.7319	97.0364	95.2040	98.9040
AUC_{0-t}	4369.4525	4510.8565	96.8653	94.9901	98.7775
C_{max}	421.9835	438.5607	96.2201	91.0845	101.6452

**Geometric mean was taken as the antilog (exponential) of the least square mean of the log-transformed data.*

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, Sitapril 100® is equivalent and interchangeable with Januvia® (sitagliptin) tablets 100 mg of Merck Sharp & Dohme Corp 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. Sitapril 100® 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>.

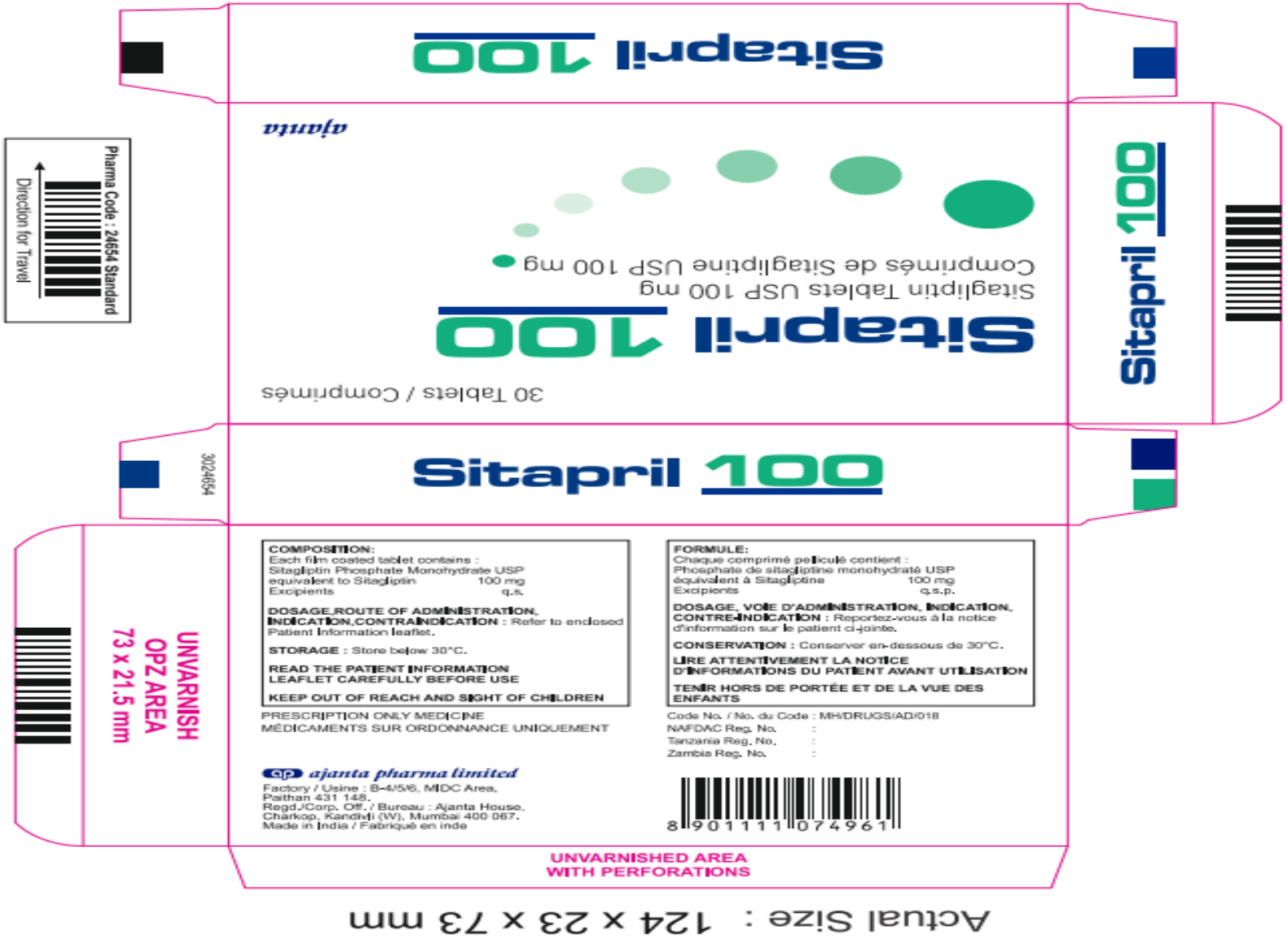
PART 5: CHANGE HISTORY

Version number	**Date**	**Description of update**	**Section(s) Modified**	**Approval date**

Annex I: Mock up label

Primary label:

Secondary label



Effective date: 03/10/2022