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MINISTRYOFHEALTH

TANZANIAMEDICINES ANDMEDICALDEVICESAUTHORITY

PUBLIC ASSESSMENT REPORT FOR PULSATYL SDK (METOPROLOL SUCCINATE 95MG EQUIVALENT TO METOPROLOL TARTRATE 100 MG) CONTROLLED RELEASE FILM COATED TABLETS

Version number 0.1
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1. Introduction

PULSATYL SDK is a generic medicine of Lopressor. PULSATYL SDK is an antihypertensive medicine belonging to C07AB02- Beta-receptor blocker, selective group. Metoprolol is a beta-1 selective beta blocker. It has a relatively greater blocking effect on beta receptors (i.e. those mediating adrenergic stimulation of heart rate and contractility and release of the fatty acids from fat stores) than on beta receptors which are chiefly involved in broncho and vasodilation. Metoprolol only exhibits insignificant membrane stabilising effect and has no agonist effect. Metoprolol reduces or blocks the stimulating effect of catecholamines (particularly released in case of physical or mental stress) on the heart. Metoprolol reduces tachycardia, decreases the cardiac output and the contractility, and lowers the blood pressure. If required, metoprolol may be administered concomitantly with a beta-2 agonist to patients with symptoms of obstructive pulmonary disease. PULSATYL SDK is approved in Tanzania for use in adults and elderly.

1.1 Product details

Registration number	TAN 21 HM 0326
Brand name	PULSATYL SDK
Generic name, strength and form	Metoprolol succinate
ATC classification	C07AB02- Beta-receptor blocker, selective
Distribution category	POM
Country of origin	Turkey
Associated product	State any other product of formulation, strength or site that is linked or associated with the product if applicable
Marketing Authorization Holder	İlko İlaç Sanayi ve Tic. A.Ş. **Address:** Veysel Karani Mah. Çolakoğlu Sok. No. 10, 34885, Sancaktepe, İstanbul-Turkey **E-Mail:** info@ilko.com.tr
Local Technical Representative	Generics & Specialities Ltd 2nd Floor, Zahra Arcade, Mindu Street, **DAR ES SALAAM.** **E-Mail:** khsrinilai@genericsgroup.net

1.2 Assessment procedure

The application for registration of PULSATYL SDK was submitted on 16th December, 2019. The product underwent full assessment. Assessment was completed in three rounds of evaluation. PULSATYL SDK was registered on 20th August, 2021.

1.3 Information for users

Visual description of the finished product	Homogeneous, white colored, round, biconvex, scored on one side film coated tablet
Primary packing material	PVC/PVDC-Alu Foil
Secondary packing materials	Carton Box
Shelf-life and storage condition	24 months Store at room temperature below 30ºC
Route of administration	Oral
Therapeutic indications	Metoprolol tartrate is indicated in the treatment of hypertension, angina pectoris, stable symptomatic chronic heart failure with impaired systolic left ventricular function, prevention of cardiac death and re-infarction after the acute phase of myocardial infarction, particularly tacardiac arrhythmias including supraventricular tachycardia, reduction of ventricular rate in extrasystoles and atrial fibrillation, prophylaxis of functional heart disorders with palpitations and migraine

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: PULSATYL SDK

Composition: Metoprolol Succinate 95 mg equivalent to Metoprolol Tartrate 100 mg, Microcrystalline Cellulose- PH 102, Microcrystalline Cellulose- PH 200, Hydrogenated vegetable oil, Colloidal silicon dioxide, Sodium stearyl fumarate

Pack size: 1 x 20’s

Manufacturing details: <batch number, manufacturing date, expiry date>
Storage conditions: Store at room temperature below 30ºC
Manufacturer address: İlko İlaç Sanayi ve Ticaret A.Ş**,** Organize Sanayi Bölgesi Kuddusi, Cad.23. Sok. No:1 Selçuklu/Konya**,** Turkey

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: PULSATYL SDK (Metoprolol Succinate 95 mg equivalent to Metoprolol Tartrate 100 mg)
Manufacturing details: <batch number, manufacturing date, expiry date>
Name of manufacturer: İlko İlaç Sanayi ve Ticaret A.Ş

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

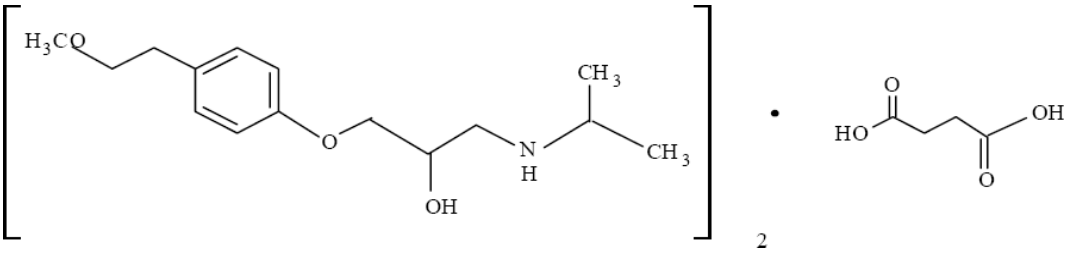
3. Scientific discussion

Quality of Active Pharmaceutical Ingredient(s)

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

General properties
Metoprolol Tartrate API is compendia in USP
Molecular formula: $(C_{15}H_{25}NO_3)_2.C_4H_6O_4$
Chemical name: 2-Propanol, 1-[4-(2 methoxyethyl)phenoxy]-3-[(1-methylethyl) amino]-, butanedioate(2:1) salt

Structure:



Metoprolol Tartrate is a white, crystalline powder that is freely soluble in water, soluble in methanol, sparingly soluble in alcohol, slightly soluble in isopropyl alcohol. In line with the Ph.Eur. monograph, there is no test for polymorphic form. This is justified, as no indications were found that polymorphic form affects the solubility and stability of the drug product, the synthetic route of the active substance is similar to already approved products and IR is able to detect differences in crystalline form

Manufacture

The API manufacturing site, Ra Chem Pharma Limited (FDF Division) Plot No-A-19/C, Road No-18, IDA Nacharam, Hydearabad-500 076, Telangana, India was noted to comply with WHO GMP requirements as evidenced by the GMP certificate issued by Drug Control Administration, Government of Telangana. Metoprolol Tartrate 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, BP, in-house standards and ICHQ3A. The parameters monitored during quality control are: Description, identification, water content, assay, dissolution, particle size distribution, residual solvents, related substances, microbial limit test. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of Metoprolol Tartrate API is 24 months when packed in double polyethylene bag in a HDPE drum and stored at 25ºC.

Quality of the Finished Pharmaceutical Product

Formulation

PULSATYL SDK (Metoprolol Succinate 95 mg equivalent to Metoprolol Tartrate 100 mg) is a Homogeneous, white colored, round, biconvex, scored on one side film coated tablet packed in PVC/PVDC-Alu Foil. PULSATYL SDK contains Metoprolol Tartrate and other ingredients listed here after Microcrystalline Cellulose- PH 102, Microcrystalline Cellulose- PH 200, Hydrogenated vegetable oil, Colloidal silicon dioxide, Sodium stearyl fumarate. 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 İlko İlaç Sanayi ve Ticaret A.Ş**,** Organize Sanayi, Bölgesi Kuddusi Cad.23. Sok. No:1 Selçuklu/Konya**,** Turkey**.** The compliance of the site to TMDA GMP standards was confirmed through site inspection on 29th -30th May, 2017.

Specifications

The FPP is compendia in BP/USP. The manufacturer controls the quality of the finished product as per BP, In House standard and ICHQ3B requirements. The parameters monitored during quality control are: <Description, identification, content uniformity, water content, average mass, dissolution, assay, related substance, microbial limit test. 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 30ºC ± 2ºC / 65% ± 5% RH for 24 months and 40 ± 2ºC/ 75% ± 5% RH Long term storage condition: 30ºC ± 2ºC / 65% ± 5% RH for 6 months. Based on the stability data presented, the approved shelf-life is 24 months when stored in PVC/PVDC – Alu Blister with a storage condition of store below 30ºC.

Safety and efficacy information

Safety and efficacy of PULSATYL SDK was established through bioequivalence trial. BE trial report number 005-13-TR was submitted.

In case of BE:

Study title	An open-label, balanced, randomized, two-treatment, two-period, two-sequence, single-dose two-way crossover oral bioequivalence study of Metoprolol Succinate 100 mg Controlled Release Film Tablets, manufactured by ilko ilac;: San. Ve Tic. A.i;l., Turkey and Beloc® ZOK 100 mg (Metoprolol succinate 100 mg) Controlled Release Film Tablets, manufactured by AstraZeneca AB, SOdertlilje Sweden in 40 normal, healthy, adult, male subjects under fasting Conditions.
Study design	A balanced, open label, balanced, randomized, two treatment, two period, two sequence, single dose, two way cross over oral bioequivalence study in normal, healthy, adult, male subjects under fasting Conditions
Study site	RA Chern Pharma Limited, Clinical Research & Biosciences Division, Plot-No.26&27, Teclmocrat Industrial Estate (TIE), Balanagar, Hyderabad-500037, INDIA. Tel. No.:040-44758595; Fax. No.: 040-44758596

Study dates	Clinical conduction: Period-I: 31th October 2013 to 03rd November 2013, Period-II: 7th November 2013 to 10th November 2013 Date of clinical phase completion: 10th November 2013 Subject Analysis: Start Date: 13th November 2013 End Date: 27th December 2013	
Primary objective	to assess the oral bioequivalence of Metoprolol Succinate 100 mg Controlled Release Film Tablets, manufactured by ilko ilac;: San. Ve Tic. A.i;l., Turkey and Beloc® ZOK 100 mg (Metoprolol succinate 100 mg) Controlled Release Film Tablets, manufactured by AstraZeneca AB, SOdertlilje Sweden in 40 normal, healthy, adult, male subjects under fasting Conditions	
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	40	
Monitored parameters	AUC, Tmax, Cmax, T1/2	
Investigational medicinal products	Test Product	Reference product
	Strength: 100 mg Batch number: 13050001 Expiry date: 05/2015	Strength: 100 mg Batch number: 008023 Expiry date: 10/2014
Analytical method	LC-MS/MS	
Statistical method		

Efficacy results are summarized as follows:

Parameter	Test	Reference	% Ratio of geometric means	90 % Confidence interval	DF	CV (%)
AUC0-t (ng.h/ml)	822.4071	804.4002	102.24	95.67-109.26	33	16.5
AUC0-inf (ng/h/ml)	853.9336	835.9899	102.15	95.18 – 109.63	33	17.6
Cmax (ng/ml)	54.1103	51.4539	105.16	97.52 - 113.41	33	18.8

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, PULSATYL SDK is equivalent and interchangeable with Beloc® ZOK 100

mg (Metoprolol succinate 100 mg) Controlled Release Film Tablets, manufactured by AstraZeneca AB 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. PULSATYL SDK 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