THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR VAROSUN (RIVAROXABAN 20 MG) FILM COATED TABLETS

Version number 01, 06/01/2023

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1. Introduction

Varosun (Rivaroxaban) 20 mg film-coated tablets is a generic medicine of Xarelto 20 mg film-coated tablets of Bayer plc is a highly selective direct factor Xa inhibitor with oral bioavailability. Inhibition of factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. Rivaroxaban does not inhibit thrombin (activated factor II) and no effects on platelets have been demonstrated.

Varosun (Rivaroxaban) 20 mg film-coated tablets is approved in Tanzania for use in:
Adults
Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack. Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

Paediatric population
Treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in children and adolescents aged less than 18 years and weighing more than 50 kg after at least 5 days of initial parenteral anticoagulation treatment.

A comprehensive description of the indications and posology is given in the SmPC.

1.1 Product details

Registration number	TAN 22 HM 0490
Brand name	Varosun 20 mg film-coated tablets
Generic name, strength and form	Rivaroxaban
ATC classification	Antithrombotic agents, direct factor Xa inhibitors, ATC code: B01AF01
Distribution category	POM
Country of origin	China
Associated product	The finished product is presented as a film-coated tablet containing 10 mg of rivaroxaban as active substance
Marketing Authorization Holder	Shanghai Fosun Pharmaceutical Development Co., L Room 350, No. 25 Kangshi road, Kangqiao town, Pudong New District (Kangqiao), Shanghai, China

Effective date: 03/10/2022

Local Technical Representative	Tridem Pharma Tanzania Limited P.O Box 23145, Plot No. 70, Keko-Mwanga Dar es Salaam

1.2 Assessment procedure

The application for registration of Varosun 20 mg film-coated tablets was submitted on 08/02/2021. The product underwent full assessment. Assessment was completed in two rounds of evaluation. Varosun 20 mg film-coated tablets was registered on 05/12/2022.

1.3 Information for users

Visual description of the finished product	Light pink film-coated tablets, round, biconvex and marked with “erye” on one side and “20” on the other side
Primary packing material	Pack of 2 x 7’s in PVC/PVDC/Alu blister pack
Secondary packing materials	Carton box alongside with a package insert
Shelf-life and storage condition	24 months Do not store above 30℃, store the tablets in blisters in the provided box/carton. Protected from light
Route of administration	Oral
Therapeutic indications	Varosun 20 mg film-coated tablets are indicated for <u>Adults</u> Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack. Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. <u>Paediatric population</u> Treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in children and adolescents aged less than 18 years and weighing more than 50 kg after at least 5 days of initial parenteral anticoagulation treatment.

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: Varosun 20 mg film-coated tablets

Composition: Each film-coated tablet contains 10 mg of rivaroxaban

Pack size: 2 x 7's tablets

Manufacturing details: batch number, manufacturing date, expiry date

Storage conditions: Do not store above 30℃, store the tablets in blisters in the provided box/carton. Protected from light

Manufacturer address: Suzhou Erye Pharmaceutical Co., Ltd. No.2 Dongqiao Anmin Road, Huangdai Town, Xiangcheng District, Suzhou, China

Unique identifier: N/A

Special warnings/precautions or instructions for use: N/A

The details of the primary pack include:

Brand name and strength: Varosun 20 mg film-coated tablets

Manufacturing details: batch number, manufacturing date, expiry date

Name of manufacturer: Suzhou Erye Pharmaceutical Co., Ltd. No.2 Dongqiao Anmin Road, Huangdai Town, Xiangcheng District, Suzhou, China

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.

Special warnings/precautions or instructions for use: This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Mock labels are (Requested)

3. Scientific discussion

Quality of Active Pharmaceutical Ingredient(s)

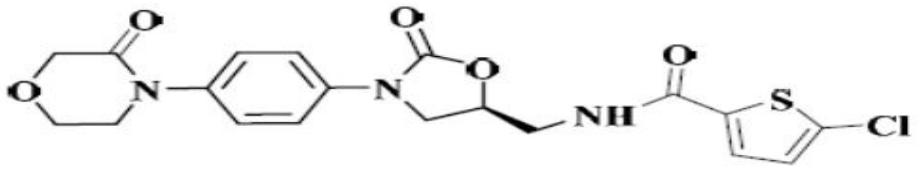
Information on quality of the API was submitted in form of Full details.

General properties
Rivaroxaban API is compendia in USP and BP Pharmacopeia.

Molecular formula: $C_{19}H_{18}ClN_3O_5S$

Chemical names:
5-chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl) phenyl]-1,3- oxazolidin-5-yl} methyl)-2-thiophene- carboxamide

Structure:



Critical physico-chemical properties are:
The active substance is a non-hygroscopic, crystalline white to yellowish solid, soluble in dimethylsulphoxide and insoluble in water. Rivaroxaban exhibits stereoisomerism due to the presence of one chiral centre. The S-isomer is the desired form. Polymorphism has been observed for rivaroxaban. The same polymorphic form is manufactured by the DMF holder and it is routinely controlled in the active substance specification by XRD.

Manufacture

The API manufacturing site, Suzhou Erye Pharmaceutical Co., Ltd.; No.2 Dongqiao Anmin Road, Huangdai Town, Xiangcheng District, Suzhou was noted to comply with WHO GMP requirements as evidenced by the GMP certificate issued by Suzhou Drug Administration, the People's Republic of China. Rivaroxaban 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 in-house standards and ICHQ3A. The parameters monitored during quality control are: appearance, solubility, identity (IR, HPLC), polymorphic (XRD), Chlorides, Loss on drying, Enantiomer, Residue on ignition, Heavy metals, assay (HPLC), related substances (HPLC), residual solvents (GC) and microbiological examination. Description and solubility are included as descriptive tests. Identification is performed by three different methods: IR, HPLC and XRD, which ensures the consistency of polymorphic form. The specification is considered acceptable. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The stability results indicate that the active substance manufactured by the proposed supplier is stable and justify the proposed retest period of 24 months when stored in the proposed container.

Quality of the Finished Pharmaceutical Product

Formulation

Varosun 20 mg film-coated tablets is Light pink film-coated tablets, round, biconvex and marked with "erye" on one side and "20" on the other side.

Varosun 20 mg film-coated tablets contains lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl methyl cellulose sodium lauryl sulfate, magnesium stearate and Purified water. The quantities of all ingredients are confirmed to be in line with the recommendations of Handbook of Pharmaceutical Excipients, Edition 8th in terms of function and quantities. Ingredient, lactose is of safety concern therefore appropriate warnings were included in the product label.

Film coating: Film coating premix (gastric) 295F640024-CN

Manufacture

The finished product was manufactured at Suzhou Erye Pharmaceutical Co., Ltd. No.2 Dongqiao Anmin Road, Huangdai Town, Xiangcheng District, Suzhou, China. The compliance of the site to TMDA GMP standards was confirmed through desk review on 17/12/2021

Specifications

The FPP is compendia in BP. The manufacturer controls the quality of the finished product as per in house standards and ICH requirements. The parameters monitored during quality control are: description, identification, (HPLC, UV), content uniformity, dissolution, assay, related substance, Enantiomer, Loss on drying and microbiological quality. 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 ± 2°C & 75% ± 5% RH for 24 months and 40 ± 2°C & 75% ± 5% RH for 6 months. All stability results met the set requirements and a shelf-life of 24 months is considered acceptable.

Safety and efficacy information

Safety and efficacy of Varosun 20 mg film-coated tablets was established through bioequivalence trial

BE trial report number Version 01 was submitted.

Study title	An open-label, balanced, randomized, single-dose, four-period, two-sequence, completely repeated and cross-over bioequivalence study of Rivaroxaban Tablets in healthy volunteers under fasting and fed conditions
Study design	an open-label, balanced, randomized, single-dose, four-period, two-sequence, completely repeated and cross-over
Study site	Clinical study site: the Third Affiliated Hospital of Qiqihar Medical University Biological sample analysis: Suzhou Guochen biotek Co., Ltd. Data management and statistical analysis: Kanghuibo (Beijing) Data Technology Co., Ltd. (seal)
Study dates	Study initiation date; April 21,2019 Study Completion date; May 23, 2019
Primary objective	To compare the difference of absorption degree and speed of Rivaroxaban Tablets test product (20mg) provided by Suzhou Erye Pharmaceutical Co., Ltd. and Rivaroxaban Tablets (20mg, trade name:Xarelto®)

	produced by Bayer Pharma AG in healthy adults under fed administration condition, and evaluate their bioequivalence	
Secondary objective	To evaluate the safety of Rivaroxaban Tablets (20mg) provided by Suzhou Erye Pharmaceutical Co., Ltd. under fed administration condition	
Number of participants	A total of 26 normal, healthy human subjects were enrolled in the study	
Monitored parameters	Tmax, Cmax, AUC0→t, AUC0→∞, AUC% Extrapolation Kel and T1/2	
Investigational medicinal products	Test Product	Reference product
	Strength: 20 mg Batch number: 0181201 Expiry date: November 2020	Strength: 20 mg Batch number: BXHRC71 Expiry date: April 6, 2020
Analytical method	LC-MS/MS method was used for the determination of plasma concentration of analyte	
Statistical method	SAS (version 9.4) software	

Efficacy results are summarized as follows:

PK parameters (Unit)	Geometric mean and ratio			Intra-subject variance of volunteers (%)		90% CI	Power %
	Test product (T)	reference product (R)	(T/R)%	CV_{WT} (%)	CV_{WR} (%)		
Ln(C_{max} (ng/mL))	472.356	473.034	99.86	13.055	15.797	95.50,104.41	>99.99
Ln(AUC_{0-t} (ng h/mL))	3259.056	3151.256	103.42	14.577	12.246	99.13,107.90	>99.99
Ln($AUC_{0-\infty}$ (ng·h/mL))	3315.340	3203.196	103.50	14.069	12.043	99.36,107.82	>99.99

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, Varosun 20 mg film-coated tablets is equivalent and interchangeable with Xarelto® 20 mg Bayer Pharma AG) 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 Varosun 20 mg film-coated tablets 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