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MINISTRYOFHEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR THROMBAN 5 AND THROMBAN 2.5 (APIXABAN 5MG AND 2.5 MG) TABLETS

Version number 1.0
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1. Introduction

THROMBAN(5 and 2.5) is a generic medicine of apixaban tablets. THROMBAN is an antithrombin medicine belonging to antithrombotic agents, direct factor Xa inhibitors group. THROMBAN exerts is activity by inhibiting the active site of factor Xa thus inhibiting free and clot-bound factor Xa, and prothrombinase activity. THROMBAN is approved in Tanzania for use in adults.

1.1 Product details

Registration number	Thromban 5: TAN 20 HM 0337 Thromban 2.5: TAN 20 HM 0336
Brand name	Thromban 5, Thromban 2.5
Generic name, strength and form	Apixaban 5 mg and 2.5 mg tablets
ATC classification	B01AF02 - antithrombotic agents, direct factor Xa inhibitors
Distribution category	POM
Country of origin	India
Associated product	NA
Marketing Authorization Holder	**Cadila Healthcare Limited** Address: Zydus Corporate Park, Scheme No. 63, Survey No 536 Khoraj (Gandhinagar), Nr. Vaishnodevi Circle, Ahmadabad Gandhinagar GJ 382 481 India E-Mail: manjul.mishra@zyduscadila.com
Local Technical Representative	**ABACUSS PHARMA (A) LIMITED** P.O. Box 12294，Dar es Salaam, Tanzania Address: 18c, Warehouse No. 4, Nyerere Road

1.2 Assessment procedure

The application for registration of Thromban was submitted on 08/02/2020. The product underwent full assessment. Assessment was completed in 2 rounds of evaluation. Thromban (5 AND 2.5) was registered on 25/09/2020.

1.3 Information for users

Visual description of the finished product	Thromban 5: Beige coloured, oval shaped, film coated tablets, debossed with “Z47” on one side and plain on the other side Thromban 2.5: White to Off white coloured, round shaped, film coated tablets debossed with ‘Z46’ on one side and plain on the other side

Primary packing material	Alu/PVC/PVDC blister
Secondary packing materials	Carton box
Shelf-life and storage condition	Below 30^0C 24 Months
Route of administration	Oral
Therapeutic indications	Prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective hip or knee replacement surgery. Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors, such as prior stroke or transient ischaemic attack (TIA); age ≥ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class ≥II). Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention ofrecurrent DVT and PE in adults

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: Thromban 5, Thromban 2.5
Composition: Apixaban 5 mg, Apixaban mg
Pack size: 3 × 10 tablets
Manufacturing details: batch number, manufacturing date, expiry date
Storage conditions: Store up to 30^0C
Manufacturer address: Cadila Healthcare Limited, Kundaim Industrial Estate, Plot No. 203 – 213, Kundaim, Goa 403 115 - India.
Unique identifier: <state the unique identification used>
Special warnings/precautions or instructions for use: This product contains lactose

The details of the primary pack include:
Brand name and strength:

Manufacturing details: <batch number, manufacturing date, expiry date>
Name of manufacturer: <name only>

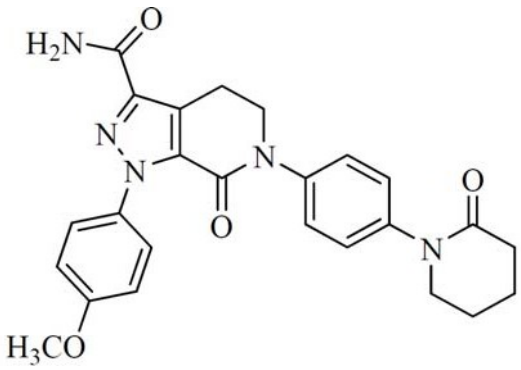
The content of the primary and secondary labels was aligned to the requirements of the Part V of the Compendium: Guidelines on Format and Content of Product Labels for Medicinal products. The label contains sufficient information for proper identification of the medicine and post marketing follow up of the product.
Describe any approved deviation to the requirements and the justification for the deviation.

3. Scientific discussion

Quality of Active Pharmaceutical Ingredient(s)

Information on quality of the API was submitted in form of APIMF.

General properties
Apixaban API is non-compendia.
Molecular formula: $C_{25}H_{25}N_5O_4$
Chemical name:
1-(4-Methoxyphenyl)-7-oxo-6-[4-(2-oxopiperidin-1-yl)phenyl]-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide
Structure:



Critical physico-chemical properties of the API were sparingly soluble in chloroform, dichloromethane and insoluble in water, it exists in four polymorphism with form-M being manufactured.

Manufacture
The API manufacturing site, MSN Laboratories Private Limited, Sy. No. 317, 320, 321, 322, 323, 604 & 605, Rudraram (Village), Patancheru (Mandal), Sangareddy District, Telangana, Pin code : 502 329, India was noted to comply with WHO GMP requirements as evidenced by the GMP certificate issued by Drug Control Administration Government of Telangana.<Molecule> 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: description, solubility, identification, water content, residue on ignition, related substances, assay, residual solvents, polymorphic identification, particle size distribution. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The re-test period of apixaban API is 48 months when packed in Low Density Polyethylene (LDPE) bag and stored at 25^0C.

Quality of the Finished Pharmaceutical Product

Formulation

Thromban 5, is a beige colored, oval shaped, film coated tablet, debossed with “Z47” on one side and plain on the other side. Thromban 2.5 is a white to off white colored, round shaped, film coated tablet, debossed with "Z46" on one side and plain on the other side. Thromban contains apixaban and other ingredients listed hereafter Hypromellose, stearic acid Tetrahydrofuran, purified water , anhydrous lactose, microcrystalline cellulose, croscarmellose sodium, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, purified water and opadry II Beige 32K570013 (HPMC 2910/Hypromellose, lactose monohydrate, titanium dioxide, triacetin , iron oxide yellow and iron oxide red) or opadry II White 32K580000 (HPMC 2910/Hypromellose, lactose monohydrate, titanium dioxide, triacetin)

. 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. Ingredient, lactose is of safety concern therefore appropriate warnings were included in the product label.

Manufacture

The finished product was manufactured at Cadila Healthcare Limited, Kundaim Industrial Estate, Plot No.203-213, Kundaim, Goa 403 115, India.The compliance of the site to TMDA GMP standards was confirmed through <site inspection/desk-review> on <date of GMP compliance>.

Specifications

The FPP is non-compendia. The manufacturer controls the quality of the finished product as per in-house and ICHQ3B requirements. The parameters monitored during quality control are: description, identification, average weight, dissolution, uniformity of dosage units, assay, related substances, water content, microbial enumeration test ,hardness and disintegration time. Compliance to the standard was established using batch analysis data and stability data.

Stability and container closure system

Stability studies were conducted on 3 batches of the finished product stored at 30 ± 2°C /75 ± 5% for 12 months and 40ºC ± 2ºC /75% ± 5% RH for 6 months. Based on the stability data presented, the approved shelf-life is 24 months when stored in Alu PVC/PVDC blisters at 30ºC.

Safety and efficacy information

Thromban 5 tablets

Safety and efficacy of Thromban 5 was established through bioequivalence trial. BE trial report number BA1686260 - 01 was submitted.

In case of BE:

Study title	An open label, randomized, two-period, two-treatment, two-sequence, crossover, balanced, single dose oral bioequivalence study of Apixaban Tablets, 5 mg of Cadila Healthcare Limited, India and ELIQUIS®' (Apixaban) Tablets, 5 mg of Bristol-Myers Squibb Company Princeton, NJ 08543, USA in healthy adult human subjects under fasting conditions	
Study design	open label, randomized, two-period, two-treatment, two-sequence, crossover, balanced, single dose oral bioequivalence study in healthy, adult, human subjects under fasting conditions was conducted to compare and evaluate the oral bioavailability of the test formulation to the reference formulation	
Study site	Cliantha Research Limited Sigma-1 Corporate, B/H. Rajpath Club, Opposite Mann Party Plot, Off. S.G Highway, Bodakdev, Ahmedabad-380 054, Gujarat, India	
Study dates	Clinical: 08/06/2016 – 20/07/2016	
Primary objective	to compare and evaluate the oral bioavailability of Apixaban Tablets, 5 mg with that of 'ELIQUIS®' (Apixaban) Tablets, 5 mg in healthy, adult, human subjects under fasting conditions	
Secondary objective	To monitor the safety of the subjects	
Number of participants	30	
Monitored parameters	Cmax, AUCt and AUCi	
Investigational medicinal products	Test Product Apixaban Tablets of Cadila Healthcare Limited, India	Reference product ELIQUIS® (Apixaban) Tablets of Bristol-Myers Squibb Company Princeton, NJ 08543, USA

	Strength: 5 mg Batch number: ME68137 Expiry date: Dec 2016	Strength: 5 mg Batch number: 5B82416A Expiry date: Jan 2018
Analytical method	AP LC/MS/MS	
Statistical method	SAS® statistical software (Version 9.4; SAS Institute Inc, USA)	

Efficacy results are summarized as follows:

Parameter	Test	Reference	% Ratio of geometric means	90 % Confidence interval	DF	CV (%)
AUC0-t (ng*hr/ mL)	1680.885	1575.305	106.70%	(103.13%;110.39%)	26	7.473
AUC0-inf (ng*hr/ mL)	1745.551	1645.035	106.11%	(102.79%;109.53%)	26	6.973
Cmax (ng/mL)	198.483	176.980	112.15%	(107.01%;117.53%)	26	10.313

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, Thromban 5 tablets is equivalent and interchangeable with ELIQUIS® (Apixaban) Tablets under acceptable in vivo experimental conditions.

Thromban 2.5 tablets

Safety and efficacy of Thromban 2.5 tablets was established through biowaiver application. Comparative dissolution report number <number> was submitted.

The biowaiver was approved based on additional strength.

Thromban 2.5 fulfilled the criteria for waiving an in-vivo bioequivalence study as per relevant TMDA guidance. Dissolution profiles of Thromban 2.5 tablets was compared to Thromban 5 tablets. At least 85% of the labelled amount of apixaban had dissolved in two media and less than 85% of the labelled amount of apixaban had dissolved in one medium . Therefore, confirming similarity and necessitating calculation of similarity factor f2 in one medium, which was noted to be above 50.

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. Thromban 5 mg and Thromban 2.5 mg tablets are 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>.

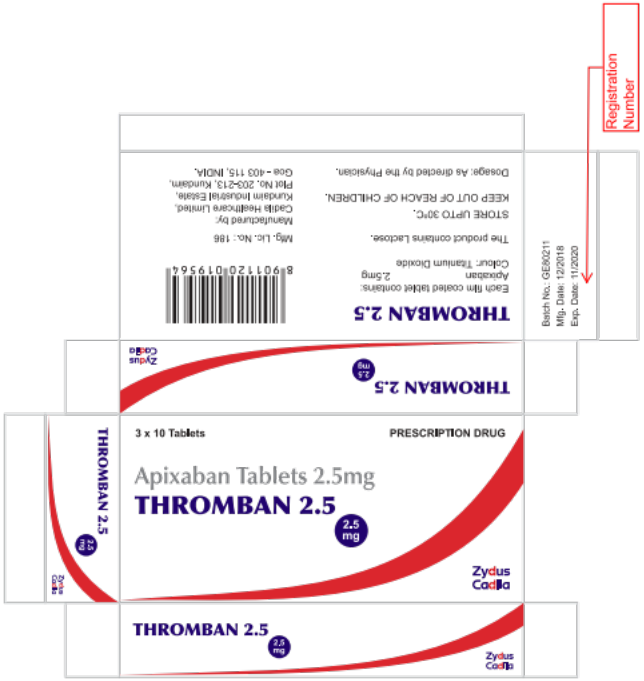
PART 5: CHANGE HISTORY

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

Annex I: Mock up label

Thromban 5:

Thromban 2.5:


Registration Number
THROMBAN 2.5
Each film coated tablet contains:
Apixaban 2.5mg
Colour: Titanium Dioxide
The product contains Lactose.
STORE UPTO 30°C.
KEEP OUT OF REACH OF CHILDREN.
Dosage: As directed by the Physician.
Mfg. Lic. No.: 186
Manufactured by:
Cadila Healthcare Limited,
Kundaim Industrial Estate,
Plot No. 203-213, Kundaim,
Goa - 403 115, INDIA.
Batch No.: GE80211
Mfg. Date: 12/2018
Exp. Date: 11/2020
3 x 10 Tablets
PRESCRIPTION DRUG
Apixaban Tablets 2.5mg
THROMBAN 2.5
2.5 mg
Zydus Cadila