THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

PUBLIC ASSESSMENT REPORT FOR GNOPAR® 40 (ENOXAPARIN SODIUM 40MG/0.4 ML) SOLUTION FOR INJECTION

Version number 1.0
21 August, 2023

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1. Introduction

GNOPAR@ 40 has been developed by Gland as a proposed biosimilar product to the reference medicinal product Lovenox® & Clexane® syringes manufactured by Sanofi-Aventis having Enoxaparin sodium as the active substance. GNOPAR@ 40 is antineoplastic medicine belongs to the pharmacotherapeutic group “monoclonal antibodies” (ATC code: L01XC07). Enoxaparin is a low-molecular-weight heparin (LMWH) obtained from unfractionated heparin (UFH). Enoxaparin binds to antithrombin III and accelerates antithrombin III activity, preferentially inhibiting the coagulation activity of factors Xa and IIa. The anticoagulant effect of enoxaparin is directly correlated with its inhibition of factor Xa activity. Factor Xa catalyses the conversion of prothrombin to thrombin; inhibition of this process by enoxaparin results in decreased thrombin concentration and the prevention of fibrin clot formation. Anti-Xa activity is used to monitor response to treatment with, and in vitro potency of, the LMWHs, including enoxaparin. The accurate determination of enoxaparin in blood or target tissues is difficult to achieve as LMWHs are mainly composed of glycosaminoglycans, which are normally present in biological tissues. Anti-Xa and anti-IIa activities are generally considered accepted pharmacodynamic (PD) surrogates to determine the pharmacokinetic properties and bioavailability of the LMWHs. GNOPAR@ 40 is approved in Tanzania for use only in adult patients.

1.1 Product details

Registration number	TAN 23 HM 251
Brand name	GNOPAR@ 40
Generic name, strength and form	Enoxaparin sodium 40mg/0.4 mL
ATC classification	Antithrombotic agent, heparin group, ATC code: B01A B05
Distribution category	POM
Country of origin	India
Associated product	GNOPAR@ 80 and GNOPAR@ 60
Marketing Authorization Holder	Shanghai Fosun Pharmaceutical Development Co., Ltd. Room 350, No.25 Kangshi Road, Kangqiao Town, Pudong New District (Kangqiao), Shanghai, China
Local Technical Representative	Triderm Pharma Tanzania Limited P.O. Box 23145, Dar es Salaam

1.2 Assessment procedure

The application for registration of GNOPAR@ 40 was submitted on DD/MM/YYYY. The product underwent full assessment. Assessment was completed in 5 (five) rounds of evaluation and the product was registered on 01/06/2023.

1.3 Information for users

Visual description of the finished product	Clear, colorless to pale yellow solution
Primary packing material	USP Type I, Clear glass syringe barrel with plunger stopper
Secondary packing materials	A printed carton box
Shelf-life and storage condition	36 months with storage conditions ‘Do not store

	above 30℃. Do not refrigerate or freeze'
Route of administration	Intravenous
Therapeutic indications	Enoxaparin Sodium Injection is used: •Prophylaxis of venous thromboembolic disease (prevention of blood clot formation in the veins), in particular after certain procedures •Prevention of thrombus formation in the extra-corporal circulation during hemodialysis •Treatment of established deep vein thrombosis •Treatment of unstable angina and non-Q-wave myocardial infarction during the acute stage, in combination with aspirin

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: GNOPAR@ 40

Composition: Each pre-filled syringe contains enoxaparin sodium 6,000 IU anti-Xa activity (equivalent to 60 mg) in 0.6 mL water for injections

Pack size: 1vial

Manufacturing details: batch number, manufacturing date and expiry date

Storage conditions: Do not store above 30℃. Do not refrigerate or freeze

Manufacturer address: physical address of release site

Unique identifier: Not applicable

Special warnings/precautions or instructions for use: Diluted solution should be used immediately

The details of the primary pack include:

Brand name and strength: GNOPAR@ 40

Manufacturing details: batch number, manufacturing date and expiry date

Name of manufacturer: Gland 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 Substance

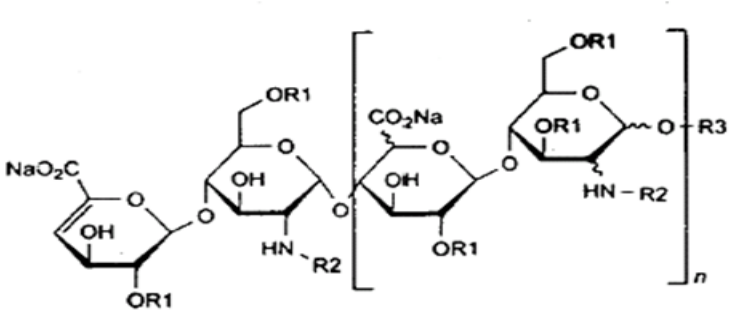
Information on quality of the active substance was submitted in form of DMF.

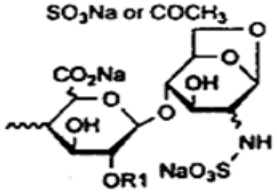
General Information

Enoxaparin sodium drug substance I is USP, BP, Ph.Eur.

Molecular weight (Relative molecular mass): The mass-average relative molecular mass ranges of Enoxaparin sodium is between 3800 and 5000, with a characteristic value of about 4500.

Structure:



	Structure at the reducing end	
	1,6-anhydro	non 1,6-anhydro
n	0 to 20	1 to 21
R1	H or SO_3Na	H or SO_3Na
R2	SO_3Na or $COCH_3$	SO_3Na or $COCH_3$
—R3		—H

General properties

Enoxaparin sodium is the sodium salt of a low-molecular-mass heparin that is obtained by alkaline depolymerisation of the benzyl ester derivative of heparin from porcine intestinal mucosa. Enoxaparin consists of a complex set of oligosaccharides that have not yet been completely characterized. Based on current knowledge, the majority of the components have a 4-enopyranose uronate structure at the non-reducing end of their chain. 15 per cent to 25 per cent of the components have a 1,6-anhydro structure at the reducing end of their chain.

It is soluble in water; insoluble in alcohol, benzene, acetone, chloroform, and ether.

Manufacture

Enoxaparin sodium active substance manufacturer is Gland Pharma Limited, D.P. Pally, Survey No.143-148,150 &151, Near Gandimaisamma 'X' Roads, Dundigal Gandimaisamma Mandal, Medchal – Malkajgiri District, Hyderabad – 500 043, Telangana, India and Gland Pharma Limited, Unit-I, Block C, Phase-I, Visakhapatnam special economic zone (VSEZ), Duvvada, Vishakapatnam - 530 049, Andhra Pradesh, India. The manufacturing complies with GMP requirements as evidenced by the GMP certificates issued by Drugs Control Administration-Andhra Pradesh. Enoxaparin sodium active substance is manufactured by fermentation 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 and ICH guidelines. The parameters monitored during quality control are: description, solubility, identification, specific absorbance, bacterial endotoxins, pH, loss on drying, nitrogen content, heavy metals, sodium content, molar ratio of sulfate to carboxylate, benzyl alcohol content, assay, anti-factor Xa activity, anti-factor IIa activity, microbial examination of non-sterile products, and residual solvents. Compliance to these specifications were established via batch analysis data and stability studies.

Stability and container closure system

The shelf-life period of Enoxaparin sodium active substance is 60 months respectively when packed in triple laminated very high barrier bag at the intended storage condition of 25 °C.

Quality of the Drug Product

Formulation

GNOPAR@ 40 is a colourless to pale brown liquid solution.

GNOPAR@ 40 contains the API Enoxaparin sodium and other ingredient is water for injections. 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 Sy. No. 143-148, 150 & 151, Near Gandimaisamma Cross Roads, D.P.Pally, Dundigal Post, Dundigal-Gandimaisamma Mandal, Medchal - Malkajgiri District, Hyderabad- 500043, Telangana, India. The compliance of the site to TMDA GMP standards was confirmed through site inspection on DD/MM/YYYY.

Specifications

The finished product is compendia. The manufacturer controls the quality of the finished product as per USP standards and ICH requirements. The parameters monitored during quality control are: description, identification, pH, bacterial endotoxins, free sulfate content, particulate matter, deliverable volume, sterility, assay (anti-factor Xa activity and anti – factor IIa activity), anti-factor Xa to anti-factor IIa ratio, residual solvents, test for break loose force, glide force (extrusion force), color of the solution, clarity of solution, and additional test for stability studies (molecular weight profile and specific absorbance). Compliance to the standard was established using batch analysis data and stability data.

Stability and container closure system

Stability studies were conducted on 3 (three) batches of the finished product stored at 30°C ± 2°C, 75 % ± 5% RH for 36 months and 40°C ± 2°C, 75 % ± 5% RH for 6 months. Based on the stability data presented, the approved shelf-life is 36 months when stored in USP Type I, Clear glass syringe barrel with plunger stopper with storage conditions ‘Do not store above 30℃. Do not refrigerate or freeze’.

Safety and efficacy information

Safety and efficacy of <brand name> was established through <bioequivalence trial/biowaiver application/clinical trial>.
<BE trial/comparative dissolution> report number <number> was submitted.
In case of BE:

Study title	
Study design	

Study site		
Study dates		
Primary objective		
Secondary objective		
Number of participants		
Monitored parameters		
Investigational medicinal products	Test Product	Reference product
	Strength: Batch number: Expiry date:	Strength: Batch number: Expiry date:
Analytical method		
Statistical method		

Efficacy results are summarized as follows:

Parameter	Test	Reference	% Ratio of geometric means	90 % Confidence interval	DF	CV (%)
AUC0-t (units)						
AUC0-inf (units)						
Cmax (units)						

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, <brand name> is equivalent and interchangeable with <comparator>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. GNOPAR@ 40 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

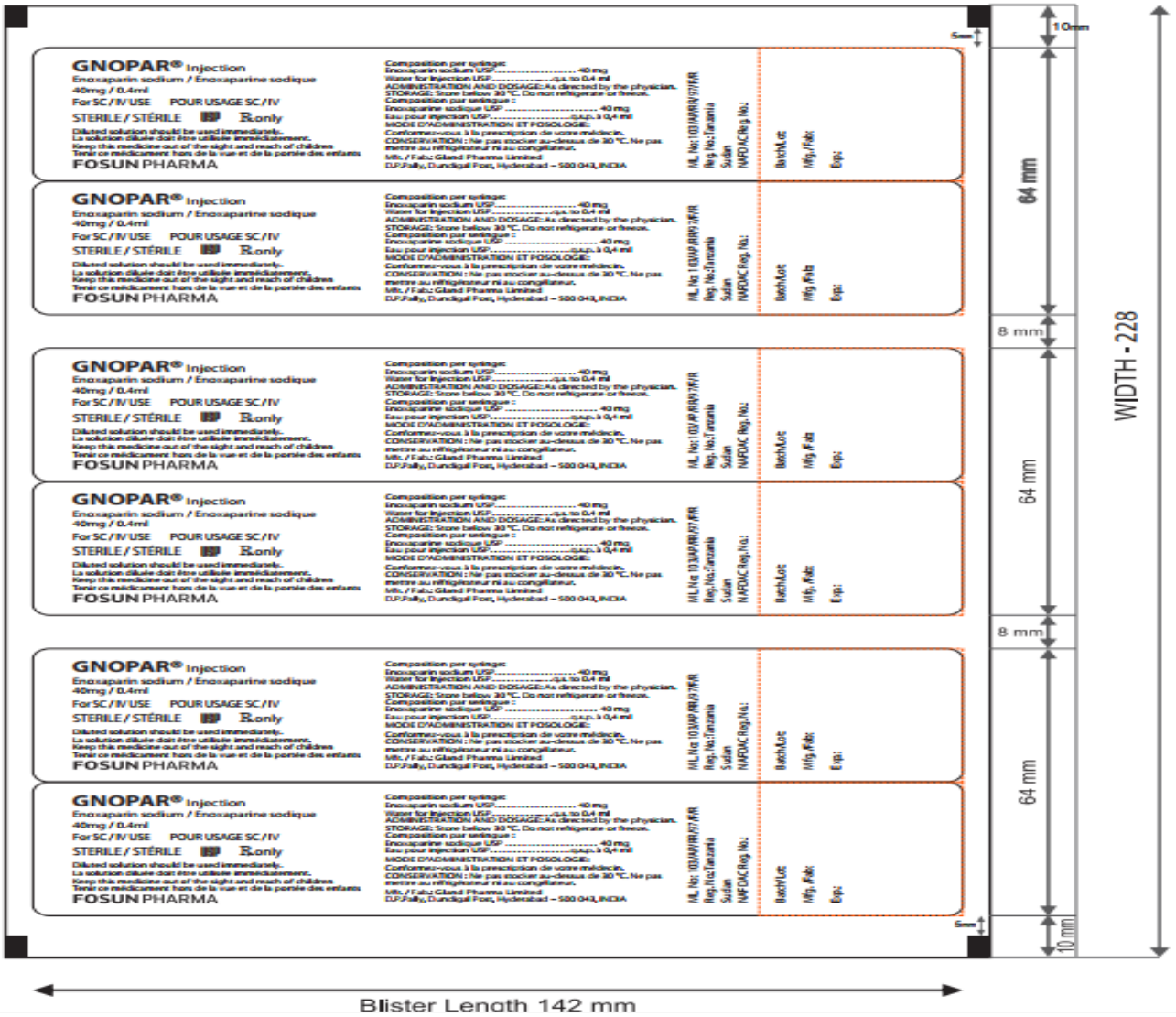
Application for renewal of registration was submitted on <DDMMYYYY>. The application was finalized in <number> rounds of evaluation. The product was confirmed to still be compliant to the standards of quality, safety and efficacy, hence registration was renewed on <DDMMYYYY>.

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: