EDA Assessment Report for Biological Medicinal Product

(Scientific Discussion)

Enoxaparin Sodium USP

Date: August 2024

Assessment report

Enoxaparin Sodium USP

Unit: Technical Assessment Unit

Administrative information:

Trade name of the medicinal product:	Enoxaparin Sodium USP, Injection
INN (or common name) of the active substance(s):	Enoxaparin sodium
Marketing Authorization holder	Nanjing King-Friend Biochemical Pharmaceutical Co. Ltd., No. 16 Xuefu Road, Nanjing High and New Technology Development Zone, Nanjing, Jiangsu 210061 - CHINA
Applied Indication(s):	Enoxaparin sodium inj. Is a low molecular weight heparin indicated for: •Prophylaxis of DVT in abdominal surgery, hip replacement surgery, knee replacement surgery, or medical patients with severely restricted mobility during acute illness •Inpatient treatment of acute DVT with or without PE. •Outpatient treatment of acute DVT without PE. •Prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction (MI)
Pharmaceutical form(s) and strength(s):	- Solution for subcutaneous injection - 40 mg and 60 mg
Route of administration	Subcutaneous injection
Approved pack	**For Enoxaparin 60mg:** Carton box containing10 prefilled syringes of 0.6ml with automatic safety device consists of USP clear colorless (type I) glass barrel, 27-guage ½ inch needle with a rubber needle shield and plugged with 1 ml dark chlorobutyl rubber plunger stopper. **For Enoxaparin 40mg:** Carton box containing 10 prefilled syringes of 0.4ml with automatic safety device consists of USP clear colorless (type I) glass barrel, 27-guage ½ inch needle with a rubber needle shield and plugged with 1 ml dark chlorobutyl rubber plunger stopper

List of abbreviations

AUC	area under the plasma concentration-time curve
CPPs	critical process paramters
CTD	Common technical document
DVT	Deep vein thrombosis
Emax	maximal activity
GMP	Good manufacturing practice
ICH	International Conference on Harmonisation
LMWH	low molecular weight heparin
MI	Myocardial infarction
PE	Pulmonary imbolism
QbD	quality by design
Sop	Standard operating procedure
TFPI	tissue factor pathway inhibitor
tmax	time to maximum activity
UFH	unfractionated heparin
USP	United states pharmacopeia

Dossier initial submission and evaluation process.

- The product was submitted for registration via 343/2021 ministerial decree.
- The dossier evaluation by the registration administration units was started on 18.12.2022 after providing all the required documents according to the "Checklist for documents of new biological products registration file".
- Full CTD along with detailed SOPs were provided.

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1. **‘General introduction about the product including brief description of the AI, its mode of action and indications:**

-Enoxaparin Sodium Injection is available as a sterile aqueous solution of 40mg/0.4mL and 60mg/0.6mL, for subcutaneous injection. The drug product is comprised of a clear, colorless to slightly yellow transparent solution, free from visible particulates, presented in clear USP Type I glass syringes. Enoxaparin sodium Injection with the two concentrations is pre-filled in the 1mL prefilled syringe.
-The composition of the drug product consists of the active ingredient Enoxaparin Sodium dissolved in Water for Injection. The pH range for Enoxaparin Sodium Injection is 5.5 to 7.5. It is aseptically filled product containing no antimicrobial preservatives.
About the product
-Enoxaparin sodium belongs to the pharmacotherapeutic group: Anticoagulant medication (blood thinner) used in the treatment and prophylaxis of thromboembolic disorders.
-Enoxaparin Sodium is one of the widely used low molecular weight heparin (LMWH) derived from unfractionated heparin (UFH) of animal origin. UFH is present in mammalian tissues and is usually obtained from the porcine intestinal mucosa. Unlike UFH, Enoxaparin Sodium can achieve therapeutic levels rapidly and safely. Enoxaparin Sodium is more stable and has more predictable characteristics and fewer fatal adverse reactions.
- The submitted data of equivalence criteria demonstrated that the Generic enoxaparin sodium drug substance is equivalent to that of Lovenox's enoxaparin in physicochemical properties, heparin source material and mode of depolymerisation, disaccharide building blocks, fragment mapping and sequence of oligosaccharide species and biochemical and biological assay

2. Quality aspects:

2.1 Introduction

2.2 Drug Substance (Active ingredient)

- **General information**

- Enoxaparin sodium is the Recommended International Nonproprietary Name (INN), U.S. Pharmacopeia Name, European Pharmacopoeia Names and United States Adopted Name (USAN)

- Enoxaparin Sodium consists of a complex set of oligosaccharides that have not yet been completely characterized. The majority of the components have a 4-enopyranose urinate structure at the non-reducing end of their chain. About 20 percent of the materials contain a 1, 6- anhydro derivative on the reducing end of the chain, the range being between 15 and 25 percent.

- **Manufacture, process controls and characterization:**

Manufacturer:

- Enoxaparin sodium is manufactured at "Nanjing King-Friend Biochemical Pharmaceutical Co. Ltd– China" and has a valid GMP certificate.

Description of Manufacturing Process and Process Controls

-Enoxaparin Sodium is manufactured in three steps (Salification, Esterification and depolymerization/ Purification) starting from Heparin Sodium API.

- The description of each stage in manufacturing process of enoxaparin sodium drug substance, flow chart, quantity of used material, operating parameter, in process control and the percentage yield had been submitted in the file

- The flow chart for each stage represent the in process control and typical yield ranges is also illustrated in the file.

Control of Materials

-Sufficient information on raw materials used in the active substance manufacturing process has been submitted.

-All raw materials are sourced from qualified suppliers. Raw materials are received, identified, tested and released according to written Standard Operating Procedures (SOPs) as required by cGMP.

-Materials used in the manufacture of drug substance are tested internally and accepted on the basis of relevant pharmacopeia testing methods & Supplier's Certificate of Analysis with reference to internal specifications.

Controls of Critical Steps and Intermediates

Process parameter and the Critical quality attribute for the manufacturing process stages had been identified. Information on the quality control of the intermediate had been submitted with description of the acceptance criteria of tests and process parameter.

Process Validation

-The Enoxaparin Sodium active substance manufacturing process has been validated adequately.

- Tests results of critical quality attribute and results for critical parameter attribute in each stage of enoxaparin sodium drug substance manufacturing had been demonstrated, aligned with the pre-determined acceptance criteria and show production process consistency.

Manufacturing Process Development.

- The submitted manufacturing process development summarizes the development of Enoxaparin sodium. The company have applied quality by design (QbD) approach principal to develop a manufacturing process with better understanding that ensures the quality of Enoxaparin sodium.

- Manufacturing process development includes the 3 stages of manufacturing process, quality attributes and trend analysis chart for each Multiple lab experiments are designed and performed for each individual stage to determine the process parameters and define critical process parameters. A lot of experiments are conducted to verify the critical process paramters (CPPs).

- In the experiment, evaluated range is set combined with the prior knowledge and the current condition of manufacturing process and an acceptable range is confirmed

Control range is set with tighten the accepted range to decrease the risk

- **Characterization**

The company characterize the structure of Enoxaparin sodium drug substance against Lovenox through performing comparability study.

- The Comparability study include the following equivalence criteria

- Equivalence of physicochemical properties
- Equivalence of heparin source material and mode of depolymerization
- Equivalence in disaccharide building blocks, fragment mapping, and sequence of oligosaccharide species
- Equivalence in biological and biochemical assays.

conclusion of comparability study: -

- The submitted data of equivalence criteria demonstrated that the Generic enoxaparin sodium drug substance is equivalent to that of Lovenox's enoxaparin in physicochemical properties, heparin source material and mode of depolymerisation, disaccharide building blocks, fragment mapping and sequence of oligosaccharide species and biochemical and biological assay.

- **Specification**

The release specification for the active substance comprises tests for physical characters, identity, purity and impurities, potency, quantity, microbiological attributes and general attributes.

The specification has been prepared in line with the requirements of requirements of USP and ICH guidelines.

- **Analytical Procedures**

All analytical procedures either pharmacopeia or in house developed were described in the submitted MA file.

- **Batch analysis**

Commercial batches representing process validation analysis data were submitted and their results comply with specification sheet and defined acceptance criteria.

- **Reference Standards or Materials**

Information regarding the reference standards used is sufficient. With respect to method validation, sufficient validation data for methods have been provided.

Container closure system

- Enoxaparin Sodium is put into double-layered low-density polyethylene bags (primary packaging) in the packaging room. After sealing, the bags are put into a PET/AL/PE bag (secondary packaging), then put into an aluminum tin (secondary packaging). The containers are sealed and labels attached. Cardboard boxes are used for external protective material.

- **Stability of drug substance**

The stability studies are conducted at long-term storage conditions as well as under accelerated conditions using Enoxaparin sodium active substance batches that were manufactured according to the intended commercial manufacturing process at the intended commercial site.

-Real time, real condition stability data of active substance for stored in a representative container closure system were provided. Data under accelerated conditions according to the ICH guidelines were provided.

-stability data of real time, stress conditions were provided.

-approved Storage Conditions of the active substance**:** stored at 25°C± 2 °C
-approved shelf life for the active substance is 36 months

2.3 Drug product:

-Description and Composition of the Drug Product:

-The drug product is a solution for injection containing Enoxaparin sodium as API. It is a clear, colourless or pale yellow solution. The finished product and its composition have been sufficiently described. The product is supplied in pre-filled syringes (PFS) and consists of a clear type I borosilicate glass syringe barrel, needle with a rubber needle shield, and a plugged with a dark chlorobutyl rubber plunger stopper.

- Pharmaceutical Development

Components of drug product

Enoxaparin Sodium, USP is a white to almost white, moderately hygroscopic powder. The solution (10% aqueous solution) is clear and not more intensely colored than degree 6 of the range of reference solutions.

-The excipients used in Product Enoxaparin Sodium Injection as Water for injection is used to dissolve the drug substance in the insert of Lovenox®. And in the manufacturing process, to decrease the risk of oxygen, nitrogen gas is filled into the syringe. The quality of nitrogen gas meets the requirement of USP NF Nitrogen.

- Formulation Development

The composition of the drug product was selected to match exactly the formulation of the reference products. No own formulation development was performed but followed the reference product formulation.

- Physicochemical and Biological Properties

Enoxaparin Sodium Injection, USP is a sterile solution of Enoxaparin Sodium in Water for Injection. It is clear and colorless to light yellow solution filled in syringe

- Manufacturing Process Development

The manufacturing process of Enoxaparin Sodium Injection, USP involves main steps of preparation, filtration and filling. In the manufacturing steps, the materials will contact stainless steel as used tanks material, silicone as pipes material, Ethylene-Propylene-Diene Monomer (EPDM) and Polytetrafluoroethylene (PTFE) as gasket material.

- Microbiological Attributes

-API and Water for Injection is controlled with Microbial limits to meet the USP requirement

- Compatibility

The product Enoxaparin Sodium Injection has filled into BD Hypak SCF (sterile clean and ready to-fill) syringe. The potential contacting components of the syringe include barrel, needle, plunger stopper and rubber needle shield. The compatibility of the solution for injection with the immediate packaging material is monitored in the stability studies.

- **Manufacture of the drug product:**

  Description of manufacturing process and process controls along with manufacturers and responsibilities.

  Manufacturer:

-The finished product manufacturing and batch release take place at Nanjing King-Friend Biochemical Pharmaceutical Co. Ltd., - CHINA
-The manufacturing method consists of several steps, namely: Compounding of Drug Solution, Filtration, Aseptic Filling, Temporary storage, Visual Inspection, Plunger and safety device and labeling, Secondary packaging and Transfer
= Based on the provided information, Appropriate IPCs have been identified and the process by which these were assigned as CQAs and CPPs has been described. Detailed information on process validation has been provided.

- Control of critical steps and intermediates

The critical steps of the Enoxaparin sodium drug product manufacturing process along with the associated in-process tests and acceptance criteria are listed in the dossier.

- Process validation and / or evaluation

-A prospective Process validation data protocol is provided in the file includes Evaluation of results of product analysis for three commercial batches.
-The results of all production steps are valid.
-Media fill protocol for lyophilized hormone department is provided in the file and the results were satisfactory.

- **Product specification:**

-The specifications for Enoxaparin Sodium Injection, 100 mg/mL and 150 mg/mL are established based on the current USP monograph for Enoxaparin Sodium Injection
-The specifications include physical characters, general tests, tests for identity, tests for puri, activity, quantity, tests for contaminants.
- Justification of the drug product specifications at the release and during stability studies are provided.

- The excipients used in the manufacture of the subject drug product meet the specifications listed in current USP/NF monograph. The excipients, Water for Injection and Nitrogen gas are manufactured internally. And the quality of the excipients are controlled by routine monitoring, and testing
-These components are controlled and tested to the standards appropriate for their intended use and function.
-no excipients of human or animal origin are used in the drug product production.
-inorganic salts impurities are a raised in manufacturing of drug product.

- **Reference Standards or Materials.**

USP reference standards are used in performing the relaease and stability testing of Enoxaparin.
-No working reference standard is used.

- **Container closure system**

-Primary Packaging:

-Container closure system of Lovenox®, as Reference List Drug (RLD) is pre-filled syringe made of USP type I borosilicate glass containers, rubber stoppers, rubber needle shield as directly contacting

materials. Enoxaparin Sodium Injection involved in the application uses the same container closure system as RLD

Stability of the drug product

Based on available stability data, the proposed shelf-life of 36 months and storage conditions (store in a refrigerator, 20° to 25°C (68° to 77°F); excursions permitted between 15° and 30°C (59° and 86°F). USP Controlled Room Temperature

Biosimilarity (Comparability exercise)

- The submitted data of equivalence criteria demonstrated that the Generic enoxaparin sodium drug substance is equivalent to that of Lovenox's enoxaparin in physicochemical properties, heparin source material and mode of depolymerisation, disaccharide building blocks, fragment mapping and sequence of oligosaccharide species and biochemical and biological assay.

3. Non-clinical and clinical aspects:

- Enoxaparin USP is a biosimilar to the low molecular weight heparin (LMWH) product Lovenox that contains a well-known and widely used active substance enoxaparin sodium.
-Enoxaparin sodium biological activity, as well as, its safety profile are well-characterized, documented in humans, and had been supported by extensive clinical use for the treatment of various thromboembolic diseases.

➢ **Pharmacology:**

- A number of in-vitro biological clotting tests (such as activated partial thromboplastin time (aPTT) and HEPTEST) and biochemical activity that assess inhibition of coagulation factors Xa (anti-FXa) and IIa (anti-FIIa) have been compared between the test Enoxaparin and the reference Lovenox aiming to assess the antithrombotic therapy of enoxaparin sodium in clinical use.
- The results indicated that the biochemical and biological assay analysis results provide robust evidence of Enoxaparin sameness. Therefore, it was demonstrated that the equivalence in biological and biochemical assays for Enoxaparin to Lovenox was established.

- Since the physicochemical and biological characterization of Enoxaparin and the reference Lovenox were performed using sensitive state-of-the-art methods and convincingly demonstrate close similarity, therefore, in vivo studies are not required as part of the comparability exercise in line with international guidelines.

➢ **Toxicology:**

- Collectively, based on the results of the in vitro comparative safety/immunogenicity studies measured the interaction with endogenous chemokine, platelet factor 4 (PF4), to characterize the potential to induce an immune response, as well as, immunomodulatory function assessment, and functional heparin-induced platelet activation (HIPA) test to predict *in vivo* immunomodulatory function, it was concluded that the risk of immunogenicity of enoxaparin **is comparable** to its reference Lovenox, and does not pose any additional risk in terms of immunogenicity.

Overall conclusion: from a pharmaceutical (anti-Xa, anti-IIa, aPTT, Heptest) and pharmacological (primary PD endpoints anti-FXa, anti-FIIa and tissue factor pathway inhibitor (TFPI) integrated into the clinical study) perspectives essential requirements for biosimilarity application were considered to be fulfilled. The absence of product candidate-specific in vivo toxicity studies was not a matter of concern from a nonclinical perspective.

Therefore, it can be concluded that biosimilarity has been demonstrated between Enoxaparin and the reference drug Lovenox.

4. Clinical aspects

- A randomized, open-Label, single-Dose, two-Period, crossover study to assess the bioequivalence of reference and test formulations of Enoxaparin 100mg following subcutaneous administration in healthy subjects bioequivalence study of Nanjing King-friend Biochemical Pharmaceutical Co., Ltd (NKF Enoxaparin) and Sanofi-Aventis (Lovenox) have been performed in healthy adult human subjects under fasting conditions (**pharmacodynamic endpoints** (anti-Xa and anti-IIa) were used as surrogate markers for circulating concentrations of low molecular weight heparins (LMWHs)) (**N**= 26)).
- **Clinical Pharmacology conclusion:**
  - **Pharmacokinetics Conclusion:**

According to EMEA/CHMP/BMWP/118264/2007 Rev. 1 guideline

Due to the heterogeneity of LMWHs, conventional pharmacokinetic studies cannot be performed**.**

- **Pharmacodynamic Conclusion:**

- The bioequivalence of test and reference formulations was determined based on E_{max}, AUC_{last} and $AUC_{0\text{-}inf}$ of anti-Xa; data for anti-IIa is provided as supportive information.
- Test and Reference formulations of enoxaparin are considered bioequivalent based upon the finding that the 90% CIs for Test: Reference for E_{max}, AUC_{last}, and AUC_{inf} for anti-Xa activity are contained within the range of 80-125%.
- Pivotal evidence for similar efficacy will be derived from the similarity demonstrated in physicochemical, functional and pharmacodynamic comparisons. A dedicated comparative efficacy trial is therefore not considered necessary. **Based on EMEA/CHMP/BMWP/118264/2007 Rev. 1 guideline.**

- **Clinical Safety conclusion:**

- Two (7.7 %) and 2 (8.3 %) subjects reported at least one treatment-emergent adverse event following administration of Test and Reference study drug, respectively.
- All AEs were considered by the investigator as mild or moderate in intensity, and all AEs were resolved prior to discharge from the study. No subject discontinued prematurely due to an AE.
- There were no serious adverse events reported during the study.
- Single subcutaneous doses of enoxaparin 100 mg were generally **safe and well tolerated** in this healthy adult and female population.

- **Clinical Immunogenicity conclusion:**

- If the impurity profile and the nature of excipients of the biosimilar do not create uncertainties with regard to their impact on safety/ immunogenicity, a safety/immunogenicity study may not be needed.

According to EMEA/CHMP/BMWP/118264/2007 Rev. 1 guideline (If immunogenicity is not evaluated in a clinical trial, the immunogenic potential of the biosimilar and the reference LMWH needs to be compared in appropriate non-clinical tests) which is already assessed in the pre-clinical report.

5. Benefit/risk conclusion

- **In conclusion the overall benefit/risk of enoxparin sodium is favourable in the following:**

- Prophylaxis of Deep Vein Thrombosis (DVT) in abdominal surgery, hip replacement surgery, knee replacement surgery, or medical patient with severely restricted mobility during acute illness.
- Inpatient treatment of acute DVT with or without pulmonary embolism.
- Outpatient treatment of acute DVT without pulmonary embolism.
- Prophylaxis of Ischemic Complications of Unstable Angina and Non-Q-Wave Myocardial Infarction.

➢ **General Conclusion and Recommendations if any:**

Based on the review of CTD modules and other supplementary documents, the product is approved.