Saudi Public Assessment Report

(Summary Report)

Enoxa®

Type of Application: New Drug Application (NDA)

Type of Product: New Biosimilar Drug

Active Pharmaceutical Ingredient(s): Enoxaparin Sodium (Low molecular weight heparin)

ATC code: B01A B05

Dosage Form: Solution for injection

Dosage Strength: 20 mg – 40 mg – 60 mg – 80 mg

Pack Size: 0.2 ml- 0.4 ml- 0.6 ml- 0.8 ml

Shelf life: 24 Months

Storage Conditions: Store below 30°C

Reference Product in SA (if applicable): NA

Marketing Authorization Holder: Les Laboratoires Medis- S.A.

Manufacturer: Les Laboratoires MédiS, Route de Tunis, Nabeul. Tunisie.

Registration No.: 2906222278 – 2906222279 – 2906222280 - 2906222281

Decision and Decision Date: Approved on 16/05/2022

Proposed Indications: ENOXA is indicated in adults for:

- Prophylaxis of venous thromboembolic disease in moderate and high-risk surgical patients, particularly those undergoing orthopedic or general surgery, including cancer surgery.
- Prophylaxis of venous thromboembolic disease in medical patients with an acute illness (such as acute heart failure, respiratory insufficiency, severe infections or

rheumatic diseases) and reduced mobility at increased risk of venous thromboembolism.

- Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), excluding PE likely to require thrombolytic therapy or surgery.
- Prevention of thrombus formation in extracorporeal circulation during hemodialysis.
- Acute coronary syndrome:
  - Treatment of unstable angina and Non-ST-segment elevation myocardial infarction (NSTEMI), in combination with oral acetylsalicylic acid.
  - Treatment of acute ST-segment elevation myocardial infarction (STEMI), including patients to be managed medically or with subsequent percutaneous coronary intervention (PCI).

Product Background

This product is considered as a new biosimilar drug, for Saudi regulatory purposes. Furthermore, this product is qualified to follow the SFDA's regular submission regulatory pathway.

The SFDA approval for Enoxa® (Enoxaparin Sodium 20 mg – 40 mg – 60 mg – 80 mg) is based on a review of the quality, safety and efficacy as summarized hereinafter:

Quality Aspects

The proposed medicine Enoxa® quality assessment was undertaken to meet the last version of GCC data requirements for human drugs submission. The submission included detailed information related to the drug substance (Enoxaparin); it is low molecular weight heparin which consists of a complex set of oligosaccharides with an average molecular weight of approximately 4,500 Dalton gives its biological activity via binding to anti-thrombin III leading to inhibition of coagulation factors IIa and Xa. Enoxaparin inhibits the coagulation factors Xa and IIa mainly; and affects other hemostatic mechanisms slightly, such as clotting time. The manufacturing process of heparin sodium and enoxaparin sodium is considered a standardized process with known test parameters. Process validation was conducted properly utilizing a sufficient number of batches representing the drug substance. Validation studies included all manufacturing stages of the drug substance: crude heparin, heparin sodium, and enoxaparin sodium to demonstrate manufacturing process consistency supported by stability studies for validation and ongoing batches using suitable stability parameters confirmed in appropriate time intervals following the relevant guidelines. Les Laboratoires MédiS is the main responsible for the manufacture of drug product, including the preparation of drug solution and formulation for all approved strengths, including 2000 IU (20 mg)/0.2 ml, 4000 IU (40 mg)/0.4 ml, 6000 IU (60mg)/0.6 ml, and 8000 IU (80 mg)/0.8 ml. The manufacturing process of the finished product is performed in several steps considering critical process parameters (CPP) and critical quality attributes (CQA) in each step, such as (density of solution, pH, integrity test of filter after filtration, and sterility). There are no issues pertaining to the drug product stability, no issues pertaining to drug substance and drug product specifications. All analytical procedures are validated in sufficient regulatory requirements that guarantee the product is well controlled with a confirmed quality.

Clinical Aspects

The clinical development program for Enoxa® consisted of one pivotal pharmacodynamics study in healthy subjects and two supportive clinical studies in patients who have benefited from total hip or knee arthroplasty:

- (942-2019) phase I Pharmacodynamics study
- (PRENOXA) phase IV Efficacy and Safety study
- (AXA) phase IV Efficacy and Safety study.

Summary of the clinical studies presented hereafter:

- 942-2019: Phase I, open-label, randomized, fasting, single injectable dose, two-treatment, two-sequence, and two-period crossover bioequivalence study to assess bioequivalence between a single injectable dose from the test product pre-filled syringes (80 mg Enoxaparin Sodium) manufactured by Les Laboratories MédiS, Tunisia versus the reference product Clexane® in 46 healthy subjects. The primary endpoints were the following pharmacokinetic parameters for anti-Xa and anti-IIa: Amax, AUEC0-t and AUEC0-∞.

Ratio and 90% Confidence Intervals (CI) of Enoxa® (Enoxaparin Sodium) 80 mg versus Clexane®, (enoxaparin sodium) 80 mg:

- **Anti-Xa**

Pharmacodynamic Parameter	Ratio (%)	90% CI
$A_{max\ (IU/mL)}$	99.86	97.08%; 102.72%
$AUC_{0\text{-}4\ (IU/mL0*hr.)}$	97.99	96.20%; 99.82%
$AUC_{0\text{-}\infty(IU/mL0*hr.)}$	100.25	97.70%; 102.86%

- **Anti-IIa**

Pharmacodynamic Parameter	Ratio (%)	90% CI
$A_{max\ (IU/mL)}$	100.11	96.23%; 104.14 %
$AUC_{0\text{-}4\ (IU/mL0*hr.)}$	94.77	91.97%; 97.64%
$AUC_{0\text{-}\infty(IU/mL0*hr.)}$	95.19	88.03%; 102.94%

- PRENOXA: Phase IV, randomized, active-controlled study to prove the non-inferiority of the Enoxa® in comparison to the Lovenox® 4000 IU in the prevention of the development of a venous thromboembolic (VTE) disease or a subclinical deep vein thrombosis (DVT) in 105 patients who have benefited from total hip or knee arthroplasty (THA or TKA). The primary endpoints were the occurrence of a clinically undeclared deep vein thrombosis.

- AXA: Phase IV, single dose, randomized, active-controlled study to compare the anticoagulant activity of two formulations of enoxaparin (Enoxa® versus Lovenox®) in a curative indication (acute coronary syndrome) and to assess the clinical and biological safety of the study

treatments in 169 patients with Acute Coronary Syndrome. The primary endpoint was the biological dosage of anti-Xa activity, 3 to 4 hours after the first injection of enoxaparin,

The clinical pharmacology, efficacy and safety results from the aforementioned studies were assessed by the SFDA efficacy and safety department. Based on the review of the submitted evidence, the benefit/risk balance of Enoxa® is considered positive. Therefore, we recommend the approval of the marketing authorization of Enoxa®.

Product Information

The approved Summary of Product Characteristics (SPC) with the submission can be found in Saudi Drug Information System (SDI) at: https://sdi.sfda.gov.sa/

The date of revision of this text corresponds to that of the Saudi PAR. New information concerning the authorized medicinal product in question will not be incorporated into the Saudi PAR. New findings that could impair the medicinal product's quality, efficacy, or safety are recorded and published at (SDI or Summary Saudi-PAR report).

For inquiry and feedback regarding Saudi PAR, please contact us at Saudi.PAR@sdfa.gov.sa