

PRODUCT MONOGRAPH  
INCLUDING PATIENT MEDICATION INFORMATION

**Pr REDESCA®**

Enoxaparin sodium solution for injection  
Solution for subcutaneous or intravenous injection, 100 mg/mL

30 mg in 0.3 mL solution in pre-filled syringes (preservative free)  
40 mg in 0.4 mL solution in pre-filled syringes (preservative free)  
60 mg in 0.6 mL solution in pre-filled syringes (preservative free)  
80 mg in 0.8 mL solution in pre-filled syringes (preservative free)  
100 mg in 1 mL solution in pre-filled syringes (preservative free)  
300 mg in 3 mL solution in multiple-dose vials (containing benzyl alcohol as preservative)

(manufacturer's standard)

**Pr REDESCA HP®**

Enoxaparin sodium solution for injection  
Solution for subcutaneous or intravenous injection, 150 mg/mL (High Potency)

120 mg in 0.8 mL solution in pre-filled syringes (preservative free)  
150 mg in 1 mL solution in pre-filled syringes (preservative free)

(manufacturer's standard)

ATC Code: B01AB05  
Anticoagulant/Antithrombotic Agent

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**RECENT MAJOR LABEL CHANGES**

|                |  |
|----------------|--|
| Not Applicable |  |
|----------------|--|

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<sup>Pr</sup>REDESCA® and <sup>Pr</sup>REDESCA HP® (enoxaparin sodium for injection) is a biosimilar biologic drug (biosimilar) to Lovenox® and Lovenox® HP

## PART I: HEALTH PROFESSIONAL INFORMATION

### 1 INDICATIONS

Indications have been granted on the basis of similarity between REDESCA / REDESCA HP and the reference biologic drugs Lovenox® and Lovenox® HP.

REDESCA (enoxaparin sodium) is indicated for:

- The prophylaxis of thromboembolic disorders (deep vein thrombosis) in patients undergoing:
  - orthopedic surgery of the hip or knee; In addition, REDESCA is indicated in hospital or after hospital discharge for long-term prevention of venous thromboembolic diseases following hip replacement surgery.
  - high risk abdominal, gynecological, or urological surgeries
  - colorectal surgery
- The prophylaxis of deep vein thrombosis (DVT) in medical patients who are at moderate risk of DVT and who are bedridden due to moderate to severe acute cardiac insufficiency (NYHA Class III or IV heart failure), acute respiratory failure revealing or complicating chronic respiratory insufficiency not requiring ventilatory support and acute respiratory infections (excluding septic shock), who require short-term prophylaxis of deep vein thrombosis.
- The prevention of thrombus formation in the extra-corporeal circulation during hemodialysis.

REDESCA is also indicated for:

- The treatment of deep vein thrombosis, with or without pulmonary embolism.
- The treatment of unstable angina or non-Q-wave myocardial infarction, concurrently with ASA.
- Treatment of acute ST-segment Elevation Myocardial Infarction (STEMI), including patients to be managed medically or with subsequent Percutaneous Coronary Intervention (PCI).

#### 1.1 Pediatrics

**Pediatrics (< 18 years of age):** No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

#### 1.2 Geriatrics

**Geriatrics (> 65 years of age):** Evidence from clinical studies and experience suggests that use in the geriatric population is associated with differences in safety or effectiveness and a brief discussion can be found in WARNINGS AND PRECAUTIONS, under Special Populations, Geriatrics.

In the clinical study conducted with the reference product, Lovenox for treatment of acute STEMI, with adjustment in dose for patients ≥75 years of age, there was no evidence of difference in efficacy between patients ≥75 years of age (n=1241) and patients less than 75 years of age (n=9015).

### 2 CONTRAINDICATIONS

REDESCA (enoxaparin sodium) is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

- Because of the content of benzyl alcohol, REDESCA, when using multiple dose vials, must not be given to newborns or premature neonates (see 7 WARNINGS AND PRECAUTIONS, under Special Populations, Pregnant Women).
- History of confirmed or suspected immunologically-mediated heparin-induced thrombocytopenia (delayed-onset severe thrombocytopenia), within the past 100 days, or in patients in whom an in vitro platelet-aggregation test in the presence of enoxaparin is positive (circulating antibodies) (see 7 WARNINGS AND PRECAUTIONS, Heparin-induced thrombocytopenia).
- Acute or subacute bacterial endocarditis.
- Active bleeding.
- Major blood clotting disorders.
- Active gastric or duodenal ulcer.
- Hemorrhagic cerebrovascular accident (except if there are systemic emboli).
- Severe uncontrolled hypertension.
- Diabetic or hemorrhagic retinopathy.
- Other conditions or diseases involving an increased risk of hemorrhage.
- Injuries to and operations on the brain, spinal cord, eyes and ears.
- Spinal/epidural anesthesia is contraindicated where repeated treatment doses of REDESCA (1 mg/kg every 12 hours or 1.5 mg/kg once daily) are required, due to an increased risk of bleeding.

## 4 DOSAGE AND ADMINISTRATION

### 4.1 Dosing Considerations

**REDESCA (enoxaparin sodium) must not be administered by the intramuscular route.**

#### Subcutaneous injection

REDESCA is administered by subcutaneous injection for the prevention of venous thromboembolic disease, treatment of deep vein thrombosis, treatment of unstable angina and non-Q-wave myocardial infarction and treatment of acute ST-segment Elevation Myocardial Infarction.

For subcutaneous use REDESCA should not be mixed with other injections or infusions.

#### IV bolus injection

For acute ST-segment Elevation Myocardial Infarction, treatment is to be initiated with a single IV bolus injection immediately followed by a subcutaneous injection.

### 4.2 Recommended Dose and Dosage Adjustment

#### **Prophylaxis in patients at risk of venous thromboembolism following hip or knee surgery (e.g. orthopedic surgery)**

The recommended dose of REDESCA is 30 mg (3000 IU) every 12 hours administered by subcutaneous injection. Provided that hemostasis has been established, the initial dose should be given 12 to 24 hours after surgery. The usual duration of treatment is from 7 to 14 days.

Treatment should be continued for as long as the risk of DVT persists. Continued therapy with REDESCA 40 mg once daily for 3 weeks following the initial phase of thromboprophylaxis in hip replacement surgery patients has been proven to be beneficial.

**Prophylaxis in patients at risk of venous thromboembolism following abdominal or colorectal Surgery**

In patients undergoing abdominal surgery who are at risk for thromboembolic complications, the recommended dose of REDESCA is 40 mg (4000 IU) once daily administered by subcutaneous injection, with the initial dose given 2 hours prior to surgery (see 7 WARNINGS AND PRECAUTIONS, General, Selection of General Surgery Patients). The usual duration of treatment is from 7 to 10 days for a maximum of 12 days.

Patients at high risk for thromboembolic complications following high risk abdominal, gynecological or urological and colorectal surgery, for cancer, who are not at risk of bleeding may benefit from an extended prophylaxis up to 4 weeks.

**Prophylaxis in Medical Patients**

In medical patients at risk for deep vein thrombosis due to severely restricted mobility during acute illness (see 7 WARNINGS AND PRECAUTIONS, General, Selection of Medical Patients), the recommended dose of REDESCA is 40 mg (4000 IU) once daily by subcutaneous injection. The usual duration of administration is 6 to 11 days.

**Treatment of Deep Vein Thrombosis, with or without Pulmonary Embolism**

REDESCA can be administered subcutaneously either as 1.5 mg/kg once daily or as twice daily injections of 1 mg/kg.

The 1.5 mg/kg once daily dose is the equivalent of 150 IU/kg and should be given at the same time every day. The single daily dose should not exceed 18,000 IU. The expected plasma anti-Xa levels during subcutaneous treatment, when enoxaparin is used as the reference standard, would be <0.3 IU anti-Xa/mL before injection and <1.7 IU anti-Xa/mL 3 - 4 hours post injection. The measurement of plasma anti-Xa circulating activities depends on the experimental conditions of the assay, particularly on the reference standard used.

In patients with complicated thromboembolic disorders (*i.e.* with increased risk of recurrent VTE such as obese patients, cancer patients or patients with symptomatic PE), a dose of 1 mg/kg administered twice daily is recommended. This is the equivalent of 100 IU/kg. The expected plasma anti-Xa levels during subcutaneous treatment, when enoxaparin is used as the reference standard, would be <0.3 IU anti-Xa/mL before injection and <1.15 IU anti-Xa/mL 3 - 4 hours post injection.

Oral anticoagulant therapy should be initiated as soon as possible, and REDESCA should be continued until a therapeutic anticoagulant effect has been achieved (INR: 2 to 3), in general for approximately 7 days.

**Treatment of Unstable Angina or non-Q-wave Myocardial Infarction**

The recommended dose of REDESCA is 1 mg/kg every 12 hours by subcutaneous injection. This is the equivalent of 100 IU/kg. The maximum dose should not exceed 10,000 IU / 12 hours. The expected plasma anti-Xa levels during subcutaneous treatment would be <0.3 IU anti-Xa/mL before injection and <1.15 IU anti-Xa/mL 3 - 4 hours after injection. Treatment should continue for a minimum of 2 days until clinical stabilization has been achieved, in general, for up to 8 days. The effect of the short-term treatment was sustained over a one-year period.

Concomitant therapy with ASA (100 to 325 mg once daily) is recommended (see 7 WARNINGS AND PRECAUTIONS, Peri-Operative considerations - Percutaneous coronary revascularisation procedures).

**Treatment of acute ST-segment Elevation Myocardial Infarction**

In patients with acute-ST-segment elevation myocardial infarction, the recommended dose of REDESCA injection is a **single IV bolus of 30 mg** plus a 1 mg/kg SC dose followed by 1 mg/kg administered SC every 12 hours (maximum 100 mg for each of the first two SC doses only, followed by 1 mg/kg SC dosing for the

remaining doses). For dosage in patients  $\geq 75$  years of age, see section below entitled Geriatrics. When administered in conjunction with a thrombolytic (fibrin specific or non-fibrin specific), REDESCA injection should be given between 15 minutes before and 30 minutes after the start of fibrinolytic therapy. All patients should receive acetylsalicylic acid (ASA) as soon as they are identified as having STEMI and maintained with 75 to 325 mg once daily unless contraindicated. The recommended duration of REDESCA injection treatment is 8 days or until hospital discharge, whichever comes first.

#### **For patients managed with Percutaneous Coronary Intervention (PCI)**

If the last REDESCA SC administration was given less than 8 hours before balloon inflation, no additional dosing is needed. If the last REDESCA SC administration was given more than 8 hours before balloon inflation, an IV bolus of 0.3 mg/kg of REDESCA injection should be administered (see 7 WARNINGS AND PRECAUTIONS, Peri-Operative considerations - Percutaneous coronary revascularisation procedures).

#### **Prevention of thrombus formation in the extra corporeal circulation during hemodialysis**

In patients with chronic renal failure, undergoing hemodialysis and that are not at high risk of hemorrhage, the following dosage is recommended:

- Optimization of dosage is required for each individual patient (different clotting stimuli are produced by different dialysis circuits and membranes, and there is inter-patient variability).
- A starting dose of enoxaparin, ranging from 0.5-1.0 mg/kg, can be administered into the arterial line of the circuit at the beginning of the dialysis session. The effect of this dose range is usually sufficient for a 4-hour session. This dose range recommendation stems from results in published clinical studies of Lovenox (see 14 CLINICAL TRIALS).
- Doses in subsequent dialysis session can be adjusted, based on the outcome of the previous dialysis.

#### **Pediatrics (< 18 years of age)**

Health Canada has not authorized an indication for pediatric use.

#### **Geriatrics ( $\geq 75$ years of age)**

For treatment of acute ST-segment Elevation Myocardial Infarction in geriatric patients  $\geq 75$  years of age, do not use an initial IV bolus. Initiate dosing with 0.75 mg/kg SC every 12 hours (maximum 75 mg for each of the first two SC doses only, followed by 0.75 mg/kg SC dosing for the remaining doses). No dose adjustment is necessary for other indications in geriatric patients unless kidney function is impaired.

#### **Use in Patients with Renal Impairment**

All patients with renal impairment treated with low molecular weight heparins should be monitored carefully.

Exposure to enoxaparin increases with degree of renal impairment. In patients with renal impairment, the increased exposure to enoxaparin has been shown to increase risk of bleeding (see 10 CLINICAL PHARMACOLOGY, Special Populations and Conditions, Renal Insufficiency).

For the prevention of thrombus formation in the extra corporeal circulation during hemodialysis, see 4 DOSAGE AND ADMINISTRATION, Prevention of thrombus formation in the extra corporeal circulation during hemodialysis.

A dosage adjustment is required for patients with severe renal impairment (creatinine clearance  $< 30$  mL/min) since enoxaparin exposure is significantly increased in this patient population. The following dosage adjustments are recommended for prophylaxis and treatment in patients with **severe** renal impairment:

- For prophylaxis in conjunction with hip or knee orthopedic surgery, the recommended dosage is **30 mg (3,000 IU) once daily**.

- For prophylaxis in conjunction with abdominal or colorectal surgery, or for prophylaxis in medical patients at risk of DVT, the recommended dosage is **20 mg (2,000 IU) or 30 mg (3,000 IU) once daily** based on individual risk/benefit assessment.
- For treatment of deep vein thrombosis, with or without pulmonary embolism, the recommended dosage is **1 mg/kg once daily**.
- For treatment of unstable angina or non-Q-wave myocardial infarction, the recommended dosage is **1 mg/kg once daily**.
- For treatment of acute ST-segment Elevation Myocardial Infarction, the recommended dosage is **30 mg-single IV bolus plus a 1 mg/kg SC dose followed by 1 mg/kg administered SC once daily**. (Maximum 100 mg for first SC dose only)
- For treatment of acute ST-segment Elevation Myocardial Infarction in geriatric patients  $\geq 75$  years of age, the recommended dosage is **1 mg/kg administered SC once daily (no initial bolus)** (Maximum 100 mg for first SC dose only)

Dosage adjustment may also need to be considered in patients who have renal characteristics close to those of patients with severe renal impairment.

### Spinal/epidural anesthesia

For patients receiving spinal/epidural anesthesia see 7 WARNINGS AND PRECAUTIONS- Peri-Operative considerations section.

## 4.4 Administration

### Subcutaneous Injection Technique

The subcutaneous injection of REDESCA should be carried out with the patient sitting or lying down in a comfortable position. Inject in the subcutaneous tissue of the anterolateral and posterolateral abdominal girdle, alternatively on the left and right sides. With the thickness of skin held between the operator's thumb and finger, introduce the entire length of the needle vertically into the skin.

### Arterial line injection

REDESCA is administered through the arterial line of a dialysis circuit for the prevention of thrombus formation in the extra-corporeal circulation during hemodialysis.

It must not be administered by the intramuscular route.

The REDESCA pre-filled disposable syringe is ready for immediate use. The use of a tuberculin syringe or equivalent is recommended when using the REDESCA multiple-dose vials to assure withdrawal of the appropriate volume of drug.

### Intravenous (Bolus) Injection Technique

REDESCA should be administered through an intravenous line. REDESCA should not be mixed or co-administered with other medications. To avoid the possible mixture of REDESCA with other drugs, the intravenous access chosen should be flushed with a sufficient amount of saline or dextrose solution prior to and following the intravenous bolus administration of REDESCA to clear the port of drug. REDESCA may be safely administered with normal saline solution (0.9%) or 5% dextrose in water.

### Initial 30-mg bolus

The initial 30-mg bolus can be administered, using the multiple dose vial or enoxaparin sodium pre-filled syringes. When graduated pre-filled syringes are used, expel the excessive volume if needed, to retain only 30 mg (0.3 ml) in the syringe. The 30-mg dose can then be directly injected into the intravenous line.

### Additional bolus for PCI when last SC administration was given more than 8 hours before balloon inflation

For patients being managed with Percutaneous Coronary Intervention (PCI), an additional IV bolus of 0.3 mg/kg is to be administered if last SC administration was given more than 8 hours before balloon inflation (see 4 DOSAGE AND ADMINISTRATION: Recommended Dose and Dosage Adjustment- For patients managed with Percutaneous Coronary Intervention (PCI)).

In order to assure the accuracy of the small volume to be injected, it is recommended to dilute the drug.

For example, to obtain a 3-mg/ml solution, using a 60-mg enoxaparin sodium pre-filled syringe, it is recommended to use a 50-ml infusion bag (*i.e.* using either normal saline solution (0.9%) or 5% dextrose in water) as follows:

Withdraw 30 ml from the infusion bag with a syringe and discard the liquid. Inject the complete contents of the 60-mg enoxaparin sodium pre-filled syringe into the 20 ml remaining in the bag. Gently mix the contents of the bag. Withdraw the required volume of diluted solution with a syringe for administration into the intravenous line.

After dilution is completed, the volume to be injected can be calculated using the following formula [Volume of diluted solution (ml) = Patient weight (kg) x 0.1] or using the table below.

The dilution should be prepared immediately before use.

**Table 1 - Volume to be injected through intravenous line after dilution is completed**

| Weight<br>[kg] | Required dose<br>(0.3 mg/kg)<br>[mg] | Volume to inject when diluted to a final<br>concentration of 3 mg/ml<br>[mL] |
|----------------|--------------------------------------|------------------------------------------------------------------------------|
| 45             | 13.5                                 | 4.5                                                                          |
| 50             | 15                                   | 5                                                                            |
| 55             | 16.5                                 | 5.5                                                                          |
| 60             | 18                                   | 6                                                                            |
| 65             | 19.5                                 | 6.5                                                                          |
| 70             | 21                                   | 7                                                                            |
| 75             | 22.5                                 | 7.5                                                                          |
| 80             | 24                                   | 8                                                                            |
| 85             | 25.5                                 | 8.5                                                                          |
| 90             | 27                                   | 9                                                                            |
| 95             | 28.5                                 | 9.5                                                                          |
| 100            | 30                                   | 10                                                                           |

**Care should be taken to ensure use of the correct formulation, either REDESCA (100 mg/mL concentration) or REDESCA HP (150 mg/mL concentration), when using these products.**

**Important:** When the REDESCA dose to be given is equivalent to the full amount of the pre-filled syringe, no attempt should be made to expel air prior to giving the injection. If the graduated syringes (60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/mL, 120 mg/0.8 mL, 150 mg/mL) are used and the dose of REDESCA has to be adjusted, it is necessary to expel the air bubble and any excess drug solution.

Under normal conditions of use, REDESCA does not modify global clotting tests of activated partial thromboplastin time (aPTT), prothrombin time (PT) and thrombin clotting time (TT). Therefore treatment can not be monitored with these tests. The plasma levels of the drug can be verified by measuring anti-Xa and anti-IIa activities.

#### 4.5 Missed Dose

Patients who miss a dose of this medication by a few hours should take it as soon as they remember. However if a patient is close to the time of the next dose, the missed dose should be skipped and they should proceed with the regular dosing schedule. Do not double dose. If a patient is unsure about how to proceed, they should contact their doctor or pharmacist.

### 5 OVERDOSAGE

Accidental overdosage following administration of REDESCA (enoxaparin sodium) may lead to hemorrhagic complications. REDESCA should be immediately discontinued, at least temporarily, in cases of significant excess dosage. In more serious cases, protamine should be administered.

The anticoagulant effect of REDESCA is inhibited by protamine. This effect may be largely neutralized by slow intravenous injection of protamine sulfate. However, even with higher doses of protamine, the aPTT may remain prolonged to a greater extent than usually seen with unfractionated heparin. Anti-factor Xa activity is never completely neutralized (maximum about 60%).

In the event that prompt reversal of the anticoagulant effects of enoxaparin is required at any time after REDESCA dosing, the following table is provided as a guide for initial use of protamine. Attending physicians confronted with a potential overdosage of enoxaparin should always use their best clinical judgment in determining the appropriate dosing regimen of protamine to be administered.

**Table 2 - Neutralization of enoxaparin by protamine**

| Protamine dose | Time Since REDESCA Dose            |                                      |                     |
|----------------|------------------------------------|--------------------------------------|---------------------|
|                | < 8 hours                          | > 8 hours and ≤ 12 hours             | >12 hours           |
|                | 1 mg protamine per 1 mg enoxaparin | 0.5 mg protamine per 1 mg enoxaparin | may not be required |

A second infusion of 0.5 mg protamine per 1 mg REDESCA may be administered if the aPTT measured 2 to 4 hours after the first infusion remains prolonged.

Particular care should be taken to avoid overdosage with protamine sulfate. Administration of protamine sulfate can cause severe hypotensive and anaphylactoid reactions. Because fatal reactions, often resembling anaphylaxis, have been reported with protamine sulfate, it should be given only when resuscitation equipment and treatment of anaphylactic shock are readily available.

For management of a suspected drug overdose, contact your regional poison control centre.

### 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognize the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

**Table 3– Dosage Forms, Strengths, Composition and Packaging**

| Route of administration                        | Dosage form/Strength                                                                                                                                                                                                                                                                                                                  | Nonmedicinal Ingredients                                                                                                           |
|------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|
| Subcutaneous injection & Intravenous injection | <p><b>REDESCA – 100 mg/mL</b><br/>Pre-filled syringes with protective shield:</p> <p>30 mg/0.3 mL<br/>40 mg/0.4 mL<br/>60 mg/0.6 mL<br/>80 mg/0.8 mL<br/>100 mg/mL</p> <p>Multiple dose vial: 300 mg/3 mL</p> <p><b>REDESCA HP– 150 mg/mL</b><br/>Pre-filled syringes with protective shield:</p> <p>120 mg/0.8 mL<br/>150 mg/ mL</p> | <p>The pre-filled syringes contain water for injection.</p> <p>The vial contains 15 mg/mL of benzyl alcohol as a preservative.</p> |

REDESCA (enoxaparin sodium solution for injection) 100 mg/mL is available in pre-filled syringes offered with a system that shields the needle after injection and in multiple dose vials:

- Single dose 30 mg/0.3 mL pre-filled syringes 27 G ½ with protective shield in box of 5 packs of 2 units, each in individual blister pack.
- Single dose 40 mg/0.4 mL pre-filled syringes 27 G ½ with protective shield in box of 5 packs of 2 units, each in individual blister pack.
- Single dose 60 mg/0.6 mL pre-filled syringes 27 G ½ with protective shield in box of 5 packs of 2 units, each in individual blister pack.
- Single dose 80 mg/0.8 mL pre-filled syringes 27 G ½ with protective shield in box of 5 packs of 2 units, each in individual blister pack.
- Single dose 100 mg/mL pre-filled syringes 27 G ½ with protective shield in box of 5 packs of 2 units, each in individual blister pack.
- Multiple dose vials 300 mg/3 mL in pack of 1 vial. Each multiple dose vial contains 45 mg benzyl alcohol as a preservative, 3 mL of solution in clear, colourless type I glass vial sealed with rubber injection stopper and white aluminium-plastic cap in a cardboard box.

The 60 mg/0.6 mL, 80 mg/0.8 mL, and the 100 mg/mL syringes are imprinted with a graduation scale of 1.0 mL with major increments of 0.1 mL and minor increments of 0.025 mL.

REDESCA HP (enoxaparin sodium solution for injection) 150 mg/mL (High Potency) is available in pre-filled syringes offered with a system that shields the needle after injection:

- Single dose 120 mg/0.8 mL pre-filled syringes 27 G ½ with protective shield in box of 5 packs of 2 units, each in individual blister pack.
- Single dose 150 mg/mL pre-filled syringes 27 G ½ with protective shield in box of 5 packs of 2 units, each in individual blister pack.

The 120 mg/0.8 mL, and the 150 mg/mL syringes are imprinted with a graduation scale of 1.0 mL with major increments of 0.1 mL and minor increments of 0.025 mL.

## Composition

REDESCA (enoxaparin sodium solution for injection) pre-filled syringe: each syringe contains 100 mg/mL of enoxaparin sodium in water for injection. The solution in the pre-filled syringe is preservative-free and intended for use as a single-dose injection.

Multiple dose vial: Each multiple dose vial contains 300 mg of enoxaparin sodium in 3.0 mL water for injection (concentration 100 mg/mL) and 45 mg benzyl alcohol as a preservative.

The pH of the REDESCA (both prefilled syringes and multiple dose vials) solution is 5.5 - 7.5 with an anti-Factor Xa activity of 9000-11000 IU per 1 ml of drug (with reference to the European Pharmacopeia). It exhibits a potency not less than 90.0 per cent and not more than 110.0 per cent of the potency stated on the label in terms of anti-FXa IU per mL. Nitrogen is used in the headspace to inhibit oxidation.

REDESCA HP (enoxaparin sodium solution for injection) pre-filled syringe: each syringe contains 150 mg/mL of enoxaparin sodium in water for injection. The solution in the pre-filled syringe is preservative-free and intended for use as a single-dose injection.

The pH of the REDESCA HP (prefilled syringes) solution is 5.5 - 7.5 with an anti-Factor Xa activity of 13500-16500 IU per 1 ml of drug (with reference to the European Pharmacopeia). It exhibits a potency not less than 90.0 per cent and not more than 110.0 per cent of the potency stated on the label in terms of anti-FXa IU per mL. Nitrogen is used in the headspace to inhibit oxidation.

## Description

REDESCA (enoxaparin sodium) is the sodium salt of a low molecular weight heparin, obtained by alkaline depolymerisation of the benzyl ester of heparin sodium from porcine intestinal mucosa. The average molecular weight of enoxaparin sodium is one third of unfractionated heparin.

## 7 WARNINGS AND PRECAUTIONS

### General

**REDESCA (enoxaparin sodium) must NOT be administered by the intramuscular route.**

**REDESCA cannot be used interchangeably (unit for unit) with unfractionated heparin (UFH) or other low molecular weight heparins (LMWHs) as they differ in their manufacturing process, molecular weight distribution, anti-Xa and anti-IIa activities, units and dosages. Special attention and compliance with instructions for use of each specific product is required during any change in treatment.**

Determination of anti-Xa levels in plasma is the only method available for monitoring REDESCA activity. The effect of REDESCA on global clotting tests such as aPTT, PT and TT is dose-dependent. At lower doses, used in prophylaxis, REDESCA does not prolong these tests. At higher doses, aPTT prolongation is observed but treatment cannot be monitored with these tests.

Measurement of peak anti-Xa levels at about 4 hours post-dose should be considered in patients at higher risk of bleeding and receiving REDESCA, such as the elderly, patients with renal impairment or the extremes of body weight, during pregnancy, or for children. At treatment doses, peak anti-Xa levels should generally be maintained at no more than 1.5 IU/mL in these patients (see 10 CLINICAL PHARMACOLOGY, and WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

### Selection of General Surgery Patients

Risk factors associated with postoperative venous thromboembolism following general surgery include history of venous thromboembolism, varicose veins, obesity, heart failure, malignancy, previous long bone

fracture of a lower limb, bed rest for more than 5 days prior to surgery, predicted duration of surgery of more than 30 minutes, age 60 years or above.

### **Selection of Orthopedic Surgery Patients**

Major orthopedic surgery carried out on the lower extremities is associated with a higher risk of VTE, and a notable percentage of patients will develop a thrombosis if they are not given prophylaxis.

Factors shown to predispose patient to VTE following major orthopedic surgery include a history of VTE, current obesity, delayed mobilization advanced age or cancer. Other risk factors that might be clinically important include congestive heart failure, chronic obstructive pulmonary disease (COPD) as well as female gender.

High risk period for VTE lasts up to 3 months after hip surgery, therefore thromboprophylaxis should start as soon as possible and continue for up to 28 to 35 days after surgery. (ACCP guidelines 2004)

### **Selection of Medical Patients**

The risk factors for the development of thrombosis in the individual medical patient are important in determining whether thromboprophylaxis is appropriate. In a clinical study with the reference product Lovenox, 40 mg once daily reduced the risk of the development of deep vein thrombosis (DVT) from 14.9% to 5.5% during the short term risk period in bedridden patients. Careful consideration should be given to the selection of patients. Patients at high risk of developing DVT or other thrombosis (such as patients with a malignant disease, a history of thrombophilia and known deficiency in antithrombin III, protein C or protein S, or APC resistance) are not candidates for therapy with REDESCA 40 mg once daily because this dose may be inadequate for those patients. Furthermore, REDESCA should not be given for thromboprophylaxis in medical patients who are bedridden due to infections with septic shock. Medical patients who require short term thromboprophylaxis for the risk of DVT due to severely restricted mobility during acute illness including moderate to severe heart failure, acute respiratory failure revealing or complicating chronic respiratory insufficiency not requiring ventilatory support, and acute respiratory infections may be selected for thromboprophylaxis with REDESCA 40 mg once daily.

The safety and efficacy of REDESCA 40 mg once daily following hospital discharge has not been established in the medical patient population. In the clinical trial mentioned above, thromboembolic events were not common following discontinuation of enoxaparin sodium 40 mg at discharge. However, a significant number of patients did require antithrombotic therapy following discharge; specifically 13.63%. During the 3 month period following discharge, less than 1% of events were serious and included deep vein thrombosis, pulmonary embolism and death which is considered to be thromboembolic in origin. Therefore, the physician should consider whether thromboprophylaxis post-discharge would be necessary for the individual patient.

### **Gastrointestinal**

REDESCA should be used with caution in patients with gastrointestinal ulceration.

### **Hematologic**

#### *Hemorrhage*

Bleeding may occur in conjunction with unfractionated heparin or low molecular weight heparin use. As with other anticoagulants, REDESCA should be used with extreme caution in patients at increased risk of hemorrhage. Bleeding can occur at any site during therapy with REDESCA. An unexpected drop in hematocrit or blood pressure should lead to a search for a bleeding site (see 8 ADVERSE REACTIONS, Bleeding).

#### *Thrombocytopenia*

Thrombocytopenia of any degree should be monitored closely.

#### *Heparin-induced thrombocytopenia (HIT)*

Heparin-induced thrombocytopenia can occur with the administration of REDESCA. Its incidence is unknown at present.

Use of enoxaparin sodium in patients with a history of immune mediated HIT within the past 100 days or in the presence of circulating antibodies is contraindicated (see **2 CONTRAINDICATIONS**). Circulating antibodies may persist several years.

Enoxaparin sodium is to be used with extreme caution in patients with a history (more than 100 days) of heparin-induced thrombocytopenia without circulating antibodies. The decision to use enoxaparin sodium in such a case must be made only after a careful benefit risk assessment and after non-heparin alternative treatments are considered.

#### *Platelets*

Platelet counts should be determined prior to the commencement of treatment with REDESCA and, subsequently, twice weekly for the duration of therapy.

Caution is recommended when administering REDESCA to patients with congenital or drug induced thrombocytopenia, or platelet defects.

#### **Hepatic/Biliary/Pancreatic**

REDESCA should be used with caution in patients with hepatic insufficiency.

#### **Immune**

During REDESCA administration, special caution is necessary in rapidly developing thrombocytopenia and severe thrombocytopenia ( $<100,000/\mu\text{L}$ ). A positive or indeterminate result obtained from in vitro tests for antiplatelet antibody in the presence of enoxaparin or other low molecular weight heparins and/or heparin would contraindicate REDESCA.

#### **Monitoring and Laboratory Tests**

Enoxaparin sodium has only a moderate prolonging effect on clotting time assays such as aPTT or thrombin time. For lab monitoring of effect, anti-Xa methods are recommended. Prolongation of aPTT during therapy with REDESCA to the same extent as with unfractionated heparin should only be used as a criteria of overdose. Dose increases aimed at prolonging aPTT to the same extent as with unfractionated heparin could cause overdose and bleeding.

REDESCA is administered subcutaneously, and therefore, the individual patient's antifactor Xa activity level will not remain within the range that would be expected with unfractionated heparin by continuous i.v. infusion throughout the entire dosing interval. In patients treated with enoxaparin 1 mg/kg twice daily for proximal deep vein thrombosis, mean peak plasma anti-Xa levels were 0.91 IU/mL. In patients given enoxaparin 1 mg/kg twice daily for acute treatment of unstable angina, peak anti-Xa activity levels were 1 - 1.1 IU/mL. At steady-state in patients given a 1.5 mg/kg qd regimen for treatment of DVT, mean peak activity was 1.7 IU anti-Xa/mL. The steady-state is practically achieved at the second or the third dose depending on the dosage regimen, once or twice daily, respectively. REDESCA should be administered as directed (see 4 DOSAGE AND ADMINISTRATION).

As with all anti-thrombotic agents, there is a risk of systemic bleeding with REDESCA administration. Consequently, therapy should not be started before primary hemostasis has been established and preferably no sooner than 12 hours after surgery (see 4 DOSAGE AND ADMINISTRATION). Care should be taken with REDESCA use in high dose treatment of newly operated patients.

After treatment is initiated, patients should be carefully monitored for bleeding complications. This may be done by regular physical examination of the patients, close observation of the surgical drain and periodic measurements of hemoglobin, and anti-factor Xa determinations. With normal prophylactic doses, enoxaparin sodium does not modify global clotting tests of activated partial thromboplastin time (aPTT), prothrombin time (PT) and thrombin clotting time (TT). Therefore, treatment cannot be monitored with these tests.

At higher doses, increases in aPTT (activated partial thromboplastin time) and ACT (activated clotting time) may occur. Increases in aPTT and ACT are not linearly correlated with increasing enoxaparin antithrombotic activity and therefore are unsuitable and unreliable for monitoring enoxaparin activity.

### **Peri-Operative Considerations**

#### *Spinal/Epidural Hematomas*

There have been cases of epidural hematomas reported with the use of low molecular weight heparins (LMWH) and spinal/epidural anesthesia or spinal puncture procedures, resulting in long term or permanent paralysis. The risk of these events is greater with higher REDESCA dosage regimens, use of post-operative indwelling catheters or the concomitant use of additional drugs affecting hemostasis such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, or other drugs affecting coagulation including glycoprotein IIb/IIIa antagonists. The risk of spinal hematoma appears to be increased by traumatic or repeated epidural or spinal puncture, history of spinal surgery or spinal deformity. REDESCA should be given after spinal/epidural anesthesia only if the anesthesiologist considers the spinal/epidural puncture as uncomplicated. Consideration should be given to delaying the next dose for 24 hours if the puncture induced trauma.

**The concomitant use of a neuraxial blockade and of an anticoagulant therapy is a clinical decision that should be made after careful assessment of the benefits and risks to the individual patient, in the following situations:**

- In patients already treated with anticoagulants, the benefits of a neuraxial blockade must be carefully balanced against the risks.
- In patients planned to undergo elective surgery with neuraxial blockade, the benefits of anticoagulant therapy must be carefully balanced against the risks.

To reduce the potential risk of bleeding associated with the concurrent use of REDESCA and epidural or spinal anesthesia/analgesia, or spinal puncture procedures, the pharmacokinetic profile of the drug should be considered (see 10 CLINICAL PHARMACOLOGY section). Placement and removal of the catheter is best performed when the anticoagulant effect of enoxaparin is low; however, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known. In the case of patients with spinal lumbar puncture, spinal anesthesia or epidural anesthesia, a minimum of 12 hours should elapse between the REDESCA injection at prophylactic doses or for 24 hours at treatment doses, and the insertion or removal of the spinal/epidural catheter or needle. A specific recommendation for timing of a subsequent LMWH dose after catheter removal cannot be made. The timing of the next dose must be based on a benefit-risk assessment considering both the risk for thrombosis and the risk for bleeding in the context of the procedure and patient risk factors.

If anticoagulation is administered in the setting of epidural/spinal anesthesia or spinal puncture procedures, continuous monitoring must be exercised to detect any signs and symptoms of neurological impairment such as midline back pain, sensory and motor deficits (numbness or weakness in lower limbs), bowel and/or bladder dysfunction (see 8 ADVERSE REACTIONS section). Patients should be instructed to inform their physician immediately if they experience any of the above signs or symptoms. If signs or

symptoms of spinal hematoma are suspected, urgent diagnosis and treatment including spinal cord decompression should be initiated immediately.

For patients with creatinine clearance <30 mL/minute, additional clinical considerations are necessary, given that elimination of enoxaparin is more prolonged; consideration should be given to doubling the timing of removal of a catheter.

### **Percutaneous coronary revascularisation procedures**

To minimize the risk of bleeding following the vascular instrumentation during the treatment of unstable angina, non-Q-wave myocardial infarction, and acute ST-segment elevation myocardial infarction, adhere precisely to the intervals recommended between REDESCA injection doses. It is important to achieve hemostasis at the puncture site after PCI. In case a closure device is used, the sheath can be removed immediately. If a manual compression method is used, it is recommended to remove the sheath 6 hours after the last IV/SC injection. If the treatment with REDESCA is to be continued, the next scheduled dose should be given no sooner than 6 to 8 hours after sheath removal. The site of the procedure should be observed for signs of bleeding or hematoma formation (see 4 DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment- Treatment of Unstable Angina or non-Q-wave Myocardial Infarction and Treatment of acute ST-segment Elevation Myocardial Infarction).

### **Renal**

REDESCA should be used with caution in patients with renal insufficiency.

REDESCA dosage should be reduced in patients with severely impaired renal function (see 10 CLINICAL PHARMACOLOGY, Special Populations and Conditions, Renal Insufficiency, and 4 DOSAGE AND ADMINISTRATION, Use in Patients with Renal Impairment).

Patients with impaired renal function should be carefully monitored because half-life for anti-Xa activity after administration of low molecular weight heparin may be prolonged in this patient population (see 4 DOSAGE AND ADMINISTRATION, Use in Patients with Renal Impairment).

In patients with renal impairment, there is an increase in exposure to enoxaparin which increases the risk of bleeding. Since exposure to enoxaparin is significantly increased in patients with severe renal impairment (creatinine clearance <30 mL/min), a dosage adjustment is recommended for both therapeutic and prophylactic dosage ranges (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and conditions, Renal Insufficiency, and 4 DOSAGE AND ADMINISTRATION, Use in Patients with Renal Impairment).

## **7.1 Special Populations**

### **7.1.1 Pregnant Women**

**The multiple dose vial of REDESCA (300 mg/3 mL) contains benzyl alcohol as a preservative. Benzyl alcohol has been associated with a potentially fatal “Gasping Syndrome” in newborns or premature neonates. Manifestations of the disease included: striking onset of gasping syndrome, metabolic acidosis, respiratory distress, gasping respirations, central-nervous system dysfunction, convulsions, intracranial hemorrhages, hypoactivity, hypotonia, hypotension, bradycardia, cardiovascular collapse and death. Because benzyl alcohol may cross the placenta, REDESCA preserved with benzyl alcohol should not be used in pregnant women.**

Teratogenic effects: As with other low molecular weight heparins, REDESCA should not be used in pregnant women unless the therapeutic benefits to the patients outweigh the possible risks. There have been reports of congenital anomalies in infants born to women who received low molecular weight

heparin during pregnancy including cerebral anomalies, limb anomalies, hypospadias, peripheral vascular malformation, fibrotic dysplasia and cardiac defects. A causal relationship has not been established nor has the incidence been shown to be higher than in the general population.

**Non-teratogenic effects:** There have been post-marketing reports of fetal death when pregnant women received low molecular weight heparins. Causality for these cases has not been established. Pregnant women receiving anticoagulants, including REDESCA, are at increased risk for bleeding. Hemorrhage can occur at any site and may lead to death of mother and/or fetus. Pregnant women receiving REDESCA should be carefully monitored. Pregnant women and women of child-bearing potential should be informed of the potential hazard to the fetus and the mother if REDESCA is administered during pregnancy.

There are also postmarketing reports of prosthetic valve thrombosis in pregnant women with prosthetic heart valves while receiving low molecular weight heparins for thromboprophylaxis. These events led to maternal death or surgical interventions.

Pregnant women with prosthetic heart valves appear to be at exceedingly high risk of thromboembolism. An incidence of thromboembolism approaching 30% has been reported in these patients, in some cases even with apparent adequate anticoagulation at treatment doses of low molecular weight heparins or unfractionated heparin. Any attempt to anticoagulate such patients should normally only be undertaken by medical practitioners with documented expertise and experience in this clinical area.

#### **7.1.2 Breast-feeding**

It is not known whether REDESCA is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when REDESCA is administered to nursing women.

#### **7.1.3 Pediatrics**

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

#### **7.1.4 Geriatrics**

Elderly patients (especially patients eighty years of age and older) receiving low molecular weight heparins are at increased risk of bleeding. Careful attention to dosing and concomitant medications, especially anti-platelet preparations, is advised. Close monitoring of elderly patients with low body weight (*e.g.* <45 kg) and those predisposed to decreased renal function is recommended.

For treatment of acute ST-segment Elevation Myocardial Infarction in geriatric patients, the incidence of bleeding complications was higher in patients ≥65 years of age as compared to younger patients (<65 years). Patients ≥75 years of age did not receive a 30-mg IV bolus prior to the normal dosage regimen and had their SC dose adjusted to 0.75 mg/kg every 12 hours (see 4 DOSAGE AND ADMINISTRATION - Recommended Dose and Dosage Adjustment, Treatment of acute ST-segment Elevation Myocardial Infarction, Geriatrics (≥75 years of age)).

#### **7.1.5 Patients with Prosthetic Heart Valves**

Cases of prosthetic valve thrombosis have been reported in patients who have received low molecular weight heparins for thromboprophylaxis. Some of these patients were pregnant women in whom

thrombosis led to maternal and/or fetal deaths. Pregnant women are at higher risk of thromboembolism (see 7 WARNINGS AND PRECAUTIONS, Use in Pregnant Women).

#### **7.1.6 Acute Coronary Disease**

When thrombolytic treatment is considered appropriate in patients with unstable angina, non-Q- wave myocardial infarction and acute ST-segment Elevation Myocardial Infarction, the concomitant use of an anticoagulant such as REDESCA may increase the risk of bleeding.

#### **7.1.7 Medical Patients**

REDESCA at a dose of 40 mg once daily should not be given for thromboprophylaxis other than deep vein thrombosis (DVT) prevention or in medical patients who, in the opinion of the attending physician, would be at a higher risk of thromboembolism (such as patients with a malignant disease, a history of thrombophilia and known deficiency in antithrombin III, protein C or protein S, or APC resistance). Furthermore, REDESCA should not be given for thromboprophylaxis in medical patients who are bedridden due to infections with septic shock. Patients with severe COPD complicated by right heart failure are candidates for another form of thromboprophylaxis. Enoxaparin sodium at a dose of 40 mg once daily has been studied in medical patients who require short term thromboprophylaxis to prevent the development of DVT while they are bedridden (6 to 11 days). If, in the opinion of the attending physician, longer thromboprophylaxis is necessary, then consideration should be given to a thromboprophylactic agent, which has been proven effective.

#### **7.1.8 Patients with Extreme Body Weight**

Safety and efficacy of low molecular weight heparins in high weight (*e.g.* > 120 kg) and low weight (*e.g.* < 45 kg) patients have not been fully determined. Individualised clinical and laboratory monitoring is recommended in these patients (see also 10 CLINICAL PHARMACOLOGY, Special Population and Conditions, Low-Weight Patients).

##### *Low-weight patients – prophylactic treatment*

An increase in exposure of enoxaparin sodium with prophylactic dosages (non-weight adjusted) has been observed in low-weight women (<45 kg) and low-weight men (<57 kg), which may lead to a higher risk of bleeding. Therefore, careful clinical monitoring is advised in these patients (see 10 CLINICAL PHARMACOLOGY, Special Population and Conditions, Low-Weight Patients).

##### *Obese patients – prophylactic treatment*

Obese patients are at higher risk for thromboembolism. The safety and efficacy of prophylactic doses in obese patients (BMI >30 kg/m<sup>2</sup>) has not been fully determined and there is no consensus for dose adjustment. These patients should be observed carefully for signs and symptoms of thromboembolism.

## **8 ADVERSE REACTIONS**

The adverse drug reaction profiles reported in clinical studies that compared REDESCA (enoxaparin sodium) to the reference biologic drug were comparable. The description of adverse reactions in this section is based on clinical experience with the reference biologic drug.

## 8.1 Adverse Reaction Overview

### Bleeding

As with any antithrombotic treatment, hemorrhagic manifestations can occur (also see 8 ADVERSE REACTIONS, Local Reactions).

The incidence of major hemorrhagic complications during enoxaparin sodium treatment has been low and generally did not differ from that observed with unfractionated heparin. Patients taking enoxaparin sodium are at risk for major bleeding complications when the plasma anti-factor Xa levels approach 2.0 IU/mL. Other risk factors associated with bleeding on therapy with heparins include a serious concurrent illness, chronic heavy alcohol consumption, use of platelet inhibiting drugs, renal failure, age and possibly, the female gender. Petechiae or easy bruising may precede frank hemorrhage. Bleeding may range from minor local hematoma to major hemorrhage. The early signs of bleeding may include epistaxis, hematuria, or melena. Bleeding may occur at any site and may be difficult to detect; such as retroperitoneal bleeding. Bleeding may also occur from surgical sites.

**Major hemorrhage, including retroperitoneal and intracranial bleeding, has been reported in association with enoxaparin sodium use, in some cases leading to fatality.**

### Local Reactions

Pain and mild local irritation may follow the subcutaneous injection of enoxaparin sodium. Rarely, hard inflammatory nodules have been observed at the injection site. Injection site hematomas are a common side effect with enoxaparin sodium occurring at a frequency of 5% or less with lower (prophylaxis) doses to 10% or more with higher (treatment) doses.

## 8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The following rates of major bleeding events have been reported during clinical trials with the reference enoxaparin sodium, Lovenox.

**Table 4 - Major Bleeding Episodes Following Abdominal and Colorectal Surgery<sup>1</sup>**

| Indications                           | Dosing Regimen                   |                          |
|---------------------------------------|----------------------------------|--------------------------|
|                                       | Enoxaparin sodium<br>40 mg qd SC | Heparin<br>5000 U q8h SC |
| <b>Abdominal Surgery<sup>2</sup></b>  | n = 555<br>23 (4%)               | n = 560<br>16 (3%)       |
| <b>Colorectal Surgery<sup>2</sup></b> | n = 673<br>28 (4%)               | n = 674<br>21 (3%)       |

<sup>1</sup> Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease  $\geq 2$  g/dL or transfusion of 2 or more units of blood products. Retroperitoneal, intraocular, and intracranial hemorrhages were always considered major.

<sup>2</sup> Enoxaparin sodium 40 mg qd SC initiated two hours prior to surgery and continued for up to 12 days after surgery.

**Table 5 - Major Bleeding Episodes Following Hip or Knee Replacement Surgery<sup>1</sup>**

| Indications                                 | Dosing Regimen                     |                            |
|---------------------------------------------|------------------------------------|----------------------------|
|                                             | Enoxaparin sodium<br>30 mg q12h SC | Heparin<br>15,000 U/24h SC |
| <b>Hip Replacement Surgery<sup>2</sup></b>  | n = 786<br>31 (4%)                 | n = 541<br>32 (6%)         |
| <b>Knee Replacement Surgery<sup>2</sup></b> | n = 294<br>3 (1%)                  | n = 225<br>3 (1%)          |

<sup>1</sup> Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease  $\geq 2$  g/dL or transfusion of 2 or more units of blood products. Retroperitoneal and intracranial hemorrhages were always considered major. In the knee replacement surgery trials, intraocular hemorrhages were also considered major hemorrhages.

<sup>2</sup> Enoxaparin sodium 30 mg every 12 hours SC initiated 12 to 24 hours after surgery and continued for up to 14 days after surgery.

NOTE: At no time point were the 40 mg once a day pre-operative and the 30 mg every 12 hours post-operative hip replacement surgery prophylactic regimens compared in clinical trials.

**Table 6 - Major Bleeding Episodes Following Hip or Knee Replacement Surgery with Extended Prophylaxis<sup>1</sup>**

| Indications                                 | Dosing Regimen                   |                           |                                   |                   |
|---------------------------------------------|----------------------------------|---------------------------|-----------------------------------|-------------------|
|                                             | Initial Prophylaxis <sup>2</sup> |                           | Extended Prophylaxis <sup>3</sup> |                   |
|                                             | Enoxaparin<br>30 mg q12h SC      | Enoxaparin<br>40 mg qd SC | Enoxaparin<br>40 mg qd SC         | Placebo<br>qd SC  |
| <b>Hip Replacement Surgery</b>              | n = 475<br>8 (1.7%)              | N = 288<br>3 (1.0%)       | n = 445<br>0 (0%)                 | N = 431<br>0 (0%) |
| <b>Knee Replacement Surgery<sup>4</sup></b> | n = 493<br>8 (1.6%)              | —                         | n = 217<br>0 (0%)                 | N = 221<br>1 (0%) |

<sup>1</sup> Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease  $\geq 2$  g/dL or transfusion of 2 or more units of blood products. Retroperitoneal and intracranial hemorrhages were always considered major.

<sup>2</sup> Initial Prophylaxis hospital phase: In the multicentre study 307, enoxaparin sodium 30 mg q12h SC for 7-10 days, initiated within 12- 24 hours postoperatively; in the single-centre study PK537, enoxaparin sodium 40 mg qd SC initiated  $12 \pm 2$  hours before surgery, repeated on the day of the surgery and continued for  $9 \pm 2$  days.

<sup>3</sup> Extended Prophylaxis outpatient phase: In the multicentre study 307, enoxaparin sodium 40 mg qd SC for 18-21 days; in the single-centre studies PK537 and ENX491001, enoxaparin sodium 40 mg qd SC  $21 \pm 2$  days.

<sup>4</sup> Initial Prophylaxis hospital phase: In the multicentre study 307, enoxaparin sodium 30 mg q12h SC for 7-10 days, initiated within 12- 24 hours postoperatively; Extended Prophylaxis outpatient phase: In the multicentre study 307.

**Table 7 - Major Bleeding Episodes in Medical Patients With Severely Restricted Mobility During Acute Illness<sup>1</sup>**

| Indications                                        | Dosing Regimen                                |                      |
|----------------------------------------------------|-----------------------------------------------|----------------------|
|                                                    | Enoxaparin sodium <sup>2</sup><br>40 mg qd SC | Placebo <sup>2</sup> |
| Medical Patients During Acute Illness <sup>3</sup> | n = 360<br>3 (<1%)                            | n = 362<br>2 (<1%)   |

<sup>1</sup> Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, (2) if the hemorrhage caused a decrease in hemoglobin of  $\geq 2$  g/dL or transfusion of 2 or more units of blood products. Retroperitoneal and intracranial hemorrhages were always considered major although none were reported during the trial.

<sup>2</sup> The rates represent major bleeding on study medication up to 24 hours after last dose.

<sup>3</sup> Usual duration of treatment 6 to 11 days.

**Table 8 - Major Bleeding Episodes in Unstable Angina and Non-Q-Wave Myocardial Infarction**

| Indication                                        | Dosing Regimen                                    |                                                    |
|---------------------------------------------------|---------------------------------------------------|----------------------------------------------------|
|                                                   | Enoxaparin sodium <sup>1</sup><br>1 mg/kg q12h SC | Heparin <sup>1</sup><br>aPTT Adjusted i.v. Therapy |
| Unstable Angina and Non-Q-Wave MI <sup>2, 3</sup> | n = 1578<br>17 (1%)                               | n = 1529<br>18 (1%)                                |

<sup>1</sup> The rates represent major bleeding on study medication up to 12 hours after last dose with treatment for up to 8 days.

<sup>2</sup> Aspirin therapy was administered concurrently (100 to 325 mg per day).

<sup>3</sup> Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease by  $\geq 3$  g/dL or transfusion of 2 or more units of blood products. Intraocular, retroperitoneal, and intracranial hemorrhages were always considered major.

**Table 9 - Major Bleeding Episodes in Treatment of Deep Vein Thrombosis with or without Pulmonary Embolism Treatment<sup>1</sup>**

| Indication                           | Dosing Regimen <sup>2</sup>          |                                      |                                          |
|--------------------------------------|--------------------------------------|--------------------------------------|------------------------------------------|
|                                      | Enoxaparin sodium<br>1.5 mg/kg qd SC | Enoxaparin sodium<br>1 mg/kg q12h SC | Heparin<br>aPTT Adjusted<br>i.v. Therapy |
| Treatment of DVT, with or without PE | n = 298<br>5 (2%)                    | n = 559<br>9 (2%)                    | n = 554<br>9 (2%)                        |

<sup>1</sup> Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease  $\geq 2$  g/dL or transfusion of 2 or more units of blood products. Retroperitoneal, intraocular, and intracranial hemorrhages were always considered major.

<sup>2</sup> All patients also received warfarin (dose-adjusted according to PT to achieve an INR of 2.0 to 3.0) commencing within 72 hours of Enoxaparin sodium or standard heparin therapy and continuing for up to 90 days. Enoxaparin sodium or standard heparin therapy was discontinued after a therapeutic oral anticoagulant effect was achieved in general about 7 days after treatment initiation.

**Table 10 - Major Bleeding Episodes in acute ST-segment Elevation Myocardial Infarction**

| Indication                                              | Dosing Regimen                                                              |                                        |
|---------------------------------------------------------|-----------------------------------------------------------------------------|----------------------------------------|
|                                                         | Enoxaparin sodium<br>Initial 30-mg IV bolus followed by 1<br>mg/kg q12h SC* | Heparin<br>aPTT Adjusted IV<br>Therapy |
| <b>Acute ST-segment Elevation Myocardial Infarction</b> | n = 10176                                                                   | n = 10151                              |
| Major bleeding (including ICH)                          | 211 (2.1%)                                                                  | 138 (1.4%)                             |
| Intracranial hemorrhages (ICH)                          | 84 (0.8%)                                                                   | 66 (0.7%)                              |

The rates represent major bleeding (including ICH) up to 30 days.

Bleedings were considered major if the hemorrhage caused a significant clinical event associated with a hemoglobin decrease by  $\geq 5$  g/dL. ICH were always considered major.

\*Patients  $\geq 75$  years of age did not receive a 30-mg IV bolus prior to the normal dosage regimen and had their SC dose adjusted to 0.75 mg/kg every 12 hours.

### Other clinically relevant adverse reactions

Other adverse reactions commonly reported in clinical trials with enoxaparin sodium were thrombocytosis, allergic reactions, hepatic enzymes increase, urticaria, pruritus, erythema, and injection site reactions.

### Adverse Reactions in LOVENOX Injection Treated Patients With acute ST-segment Elevation Myocardial Infarction

In a clinical trial in patients with acute ST-segment elevation myocardial infarction, the only additional possibly related adverse reaction that occurred at a rate of at least 0.5% in the enoxaparin group was thrombocytopenia (1.5%).

#### 8.2.1 Clinical Trial Adverse Reactions (Pediatrics)

##### Adverse Reactions in Pediatric Patients

The safety of enoxaparin sodium has not been established in pediatric patients.

#### 8.5 Post-Market Adverse Reactions

##### Blood and Lymphatic System Disorders

- **Heparin-induced Thrombocytopenia**

Severe immunologically-mediated thrombocytopenia has been observed rarely with the reference product enoxaparin sodium use, resulting in arterial and/or venous thrombosis or thromboembolism (see 7 WARNINGS AND PRECAUTIONS, Hematologic, Thrombocytopenia, Platelets and 7 WARNINGS AND PRECAUTIONS, Immune). In some cases thrombosis was complicated by organ infarction or limb ischemia.

- Thrombocytopenia
- Hemorrhagic anemia
- Eosinophilia

##### Hepatobiliary disorders

- **Liver**

Transient, asymptomatic elevations of liver transaminases (AST and ALT) to greater than three times the upper limit of normal has been observed in up to 6% of patients taking the reference product enoxaparin sodium. This is a consistent finding with all members of the LMWH class, as well as with unfractionated heparin. The mechanism associated with the increased levels of liver transaminases

has not been elucidated. No consistent irreversible liver damage has been observed. Transaminase levels returned to normal within 3 to 7 days after discontinuation of enoxaparin.

- Hepatocellular injury
- Cholestatic liver injury

#### **Immune System Disorders**

- **Hypersensitivity**  
Hypersensitivity reactions, including angioedema and anaphylactic/anaphylactoid reaction including shock have been observed rarely with unfractionated heparin and low molecular weight heparins including enoxaparin.

#### **Metabolism and nutrition disorders**

- **Hyperkalemia**  
Cases of hyperkalemia have been reported with heparins and Low Molecular Weight Heparins.

#### **Musculoskeletal and connective tissue disorders**

- **Skeletal Effects**  
Use of low molecular weight heparins over extended periods has been reported to be associated with development of osteopenia.
- Osteoporosis following long-term therapy (greater than 3 months).

#### **Nervous System Disorders**

- Headache

#### **Skin and subcutaneous tissue disorders**

- Skin rash (including bullous eruptions), purpura, and allergic reactions occur with all low molecular weight heparins. Skin necrosis is rare, usually occurring at the injection site and preceded by purpura or erythematous plaques, infiltrated and painful. In case such reaction is observed, treatment with enoxaparin sodium must be discontinued. Very rare cases of hypersensitivity cutaneous vasculitis have been reported. These cases may include leukocytoclastic vasculitis. Enoxaparin sodium should be discontinued in patients showing local or systemic allergic responses.
- Alopecia

#### **Vascular Disorders**

- Cases of spinal hematoma (or neuraxial hematoma) have been reported with the concurrent use of enoxaparin sodium as well as spinal/epidural anesthesia or spinal puncture. These reactions have resulted in varying degrees of neurologic injuries including long-term or permanent paralysis (see 7 WARNINGS AND PRECAUTIONS, Peri-Operative considerations, Spinal/Epidural Hematomas).

## **9 DRUG INTERACTIONS**

### **9.4 Drug-Drug Interactions**

It is recommended that agents which affect hemostasis should be discontinued prior to REDESCA (enoxaparin sodium) therapy unless strictly indicated. If the combination is indicated, REDESCA should be used with careful clinical and laboratory monitoring when appropriate.

REDESCA should be used with caution in patients receiving oral anticoagulants, platelet inhibitors, non-steroidal anti-inflammatories and thrombolytic agents because of increased risk of bleeding. Aspirin, unless contraindicated, is recommended in patients treated for unstable angina or non-Q-wave

myocardial infarction and acute ST-segment Elevation Myocardial Infarction (see 4 DOSAGE AND ADMINISTRATION)

### 9.7 Drug-Laboratory Test Interactions

Since enoxaparin sodium use may be associated with a rise in hepatic transaminases, this observation should be considered when liver function tests are assessed (see 8 ADVERSE REACTIONS, Post Market Adverse Drug Reactions, Liver).

## 10 CLINICAL PHARMACOLOGY

### 10.1 Mechanism of Action

REDESCA (enoxaparin sodium) is a low molecular weight heparin fragment, which is obtained by controlled depolymerization of natural heparin from porcine intestinal mucosa. It possesses antithrombotic action. Enoxaparin is composed of molecules with and without a specially characterized pentasaccharide, the antithrombin binding site, that is essential for high affinity binding to the plasma protein antithrombin (formerly referred to as antithrombin III). With a molecular weight range of 3,800 - 5,000 daltons (versus 15,000 daltons for heparin), the enoxaparin molecule is too small to bind simultaneously to thrombin and antithrombin, the primary anticoagulant factor in blood.

The mechanism of action of enoxaparin is antithrombin-dependent. It acts mainly by accelerating the rate of the neutralization of certain activated coagulation factors by antithrombin, but other mechanisms may also be involved. Enoxaparin potentiates preferentially the inhibition of coagulation factors Xa and IIa and only slightly affects other hemostatic mechanisms such as clotting time. The antithrombotic effect of enoxaparin is well correlated to the inhibition of factor Xa.

The ratio of anti-Xa/anti-IIa activity is greater than 4 with enoxaparin (whereas this ratio is equal to 1 with heparin). This dissociation between anti-Xa and anti-IIa activities has been shown in experimental models with an antithrombotic activity comparable to that of heparin while the bleeding effect is reduced. In man, clinical trials have not shown a causal relationship between the ratio of anti-Xa/anti-IIa activity and clinical/pharmacological effect.

### 10.2 Pharmacodynamics

Enoxaparin cannot be measured directly in the bloodstream. Rather the effect on clotting mechanisms is measured. Heparin dosage is monitored by both prolongation of aPTT and by anti-Xa activity. For enoxaparin, the aPTT may not be significantly prolonged relative to unfractionated heparin at prophylactic doses, and at therapeutic doses aPTT prolongation is not used to measure the therapeutic effect of enoxaparin. Enoxaparin potency is described in international anti-Xa units (*e.g.*, 1 mg of enoxaparin is equivalent to 100 IU of anti-Xa).

In the *in vitro* purified system, enoxaparin sodium has a high anti-Xa activity (approximately 100 IU/mg) and low anti-IIa or anti thrombin activity (approximately 28 IU/mg). These anticoagulant activities are mediated through anti-thrombin III (ATIII) resulting in anti- thrombotic activities in humans.

Beyond its anti-Xa/IIa activity, further anti-thrombotic and anti-inflammatory properties of enoxaparin have been identified in healthy subjects and patients as well as in non-clinical models. These include ATIII-dependent inhibition of other coagulation factors like factor VIIa, induction of endogenous Tissue Factor Pathway Inhibitor (TFPI) release as well as a reduced release of von Willebrand factor (vWF) from the vascular endothelium into the blood circulation. These factors are known to contribute to the overall anti-thrombotic effect of enoxaparin.

### 10.3 Pharmacokinetics

#### Absorption:

The pharmacokinetics of enoxaparin have been studied on the basis of plasma levels of anti-Xa activity. The mean absolute bioavailability of enoxaparin, when given subcutaneously, is about 92% in healthy volunteers.

The mean peak plasma anti-Xa activity is observed 3 to 5 hours after subcutaneous injection. Levels of approximately 0.2, 0.4, 1.0 and 1.3 anti-Xa IU/mL were seen in healthy volunteers, following a single subcutaneous administration of 20 mg, 40 mg, 1 mg/kg and 1.5 mg/kg, respectively.

Enoxaparin pharmacokinetics appear to be linear over the recommended dosage ranges. After repeated subcutaneous administration of the 1 mg/kg twice daily regimen, the steady-state is reached from Day 3 to 4 with mean exposure about 65% higher than after a single dose. Mean peak and trough levels of about 1.2 and 0.52 IU/mL respectively were seen with this regimen.

A 30 mg IV bolus immediately followed by a 1 mg/kg SC every 12 hours provided initial peak anti-Factor Xa levels of 1.16 IU/mL (n=16) and average exposure corresponding to 88% of steady-state levels. Steady state is achieved on the second day of treatment.

#### Distribution:

The volume of distribution of enoxaparin is about 5 liters. Following subcutaneous dosing, the apparent clearance of enoxaparin is approximately 15 mL/min.

Information from a clinical trial with a very small number of volunteers indicates that enoxaparin, as detected by anti-factor Xa activity, does not appear to cross the placental barrier, at least during the second trimester of pregnancy.

#### Metabolism:

Enoxaparin is metabolized in the liver by desulfation and depolymerization.

#### Elimination:

Elimination appears monophasic with a half-life of about 4 hours after a single subcutaneous dose and about 7 hours after repeated dosing, in healthy volunteers.

The main route of elimination is via the kidney. Renal clearance of active fragments represents about 10% of the administered dose and total renal excretion of active and non-active fragments 40% of the dose.

#### Pharmacokinetic interaction:

No pharmacokinetic interaction was observed between enoxaparin and thrombolytics when administered concomitantly.

### Special Populations and Conditions

#### Geriatrics:

Based on the results of a population pharmacokinetic analysis, the enoxaparin kinetic profile is not different in elderly subjects compared to younger subjects when renal function is normal. However, since renal function is known to decline with age, elderly patients may show reduced elimination of enoxaparin (see 7 WARNINGS AND PRECAUTIONS, Renal and Special Populations, Geriatrics).

#### Low-Weight Patients:

When non-weight-adjusted dosing was administered, after a single-subcutaneous 40 mg dose, anti-Xa exposure was observed to be 52% higher in low-weight women (<45 kg) and 27% higher in low-weight

men (<57 kg) when compared to normal weight control subjects, which may lead to a higher risk of bleeding (see 7 WARNINGS AND PRECAUTIONS, Special Populations, Patients with Extreme Body Weight).

**Renal Insufficiency:**

A linear relationship between anti-Xa plasma clearance and creatinine clearance at steady-state has been observed, indicating decreased clearance of enoxaparin in patients with reduced renal function.

Anti-Xa exposure at steady-state, represented by AUC, is increased about 34% in mild renal impairment (creatinine clearance 50-80 mL/min), about 72% in moderate renal impairment (creatinine clearance 30-50 mL/min), and about 95% in severe renal impairment (creatinine clearance <30 mL/min) upon administration of enoxaparin 1.5 mg/kg once daily sc for 4 days. Anti-Xa exposure at steady-state is increased about 33% in mild renal impairment, about 46% in moderate and about 97% in severe renal impairment upon administration of enoxaparin 1 mg/kg bid sc for 4 days. When enoxaparin was administered at a fixed, prophylaxis dose of 40 mg once daily sc for 4 days, the anti-Xa exposure increased by about 20% in mild renal impairment, about 21% in moderate renal impairment, and about 65% in severe renal impairment (see 7 WARNINGS AND PRECAUTIONS, Renal, and DOSAGE AND ADMINISTRATION, Use in Patients with Renal Impairment).

The half-life for anti-Xa activity in patients with impaired renal function is much longer than for people with normal renal function ( $t_{1/2}$  = 5.12 h in patients with chronic renal failure vs 2.94 h in young healthy volunteers) when enoxaparin was administered intravenously.

## 11 STORAGE, STABILITY AND DISPOSAL

**Temperature:**

Store below 25°C. Do NOT freeze.

**Others:**

Do not store the multiple dose vials for more than 28 days after the first use.

## 12 SPECIAL HANDLING INSTRUCTIONS

REDESCA (enoxaparin sodium) is usually administered as a subcutaneous injection, which means the injection is made just under the surface of the skin. For some conditions, REDESCA may be administered as an intravenous (IV) injection. REDESCA must NOT be administered by the intramuscular route.

Patients and caregivers should be instructed in the technique of proper injection as well as the syringe disposal and be cautioned against reuse of these items.

## PART II: SCIENTIFIC INFORMATION

### 13 PHARMACEUTICAL INFORMATION

#### Drug Substance

Proper name: Enoxaparin sodium

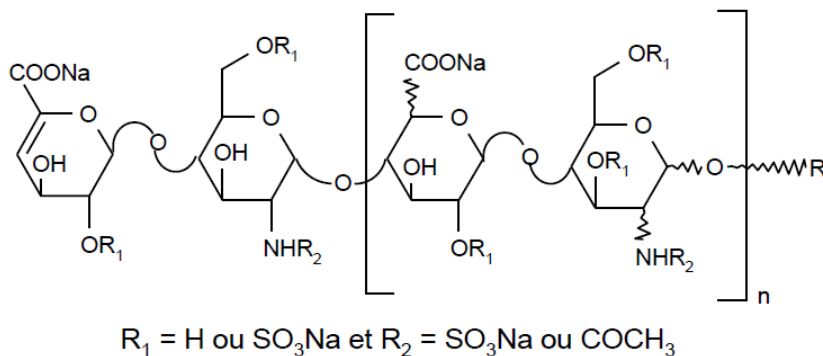
Chemical name: Enoxaparin sodium is the sodium salt of a low molecular weight heparin, obtained by alkaline depolymerisation of the benzyl ester of heparin sodium from porcine intestinal mucosa. The average molecular weight of enoxaparin sodium is one third of unfractionated heparin.

Enoxaparin sodium is a mixture of sulfated polysaccharide chains which vary in length and are made of repeating disaccharide units; the complex set of oligosaccharides have not yet been completely characterised. The disaccharide monomer consists of one molecule of uronic acid and one molecule of D-glucosamine, linked in the 1-4 position. Uronic acid can be either D glucuronic acid or L-iduronic acid, and in addition, L-iduronic acid can be sulfated on position 2. Glucosamine can be N-sulfated, N-acetylated, 6-O-sulfated, or 3-O-sulfated.

Based on current knowledge, the majority of the components have a 4-enopyranose uronate structure at the non-reducing end of their chain. About 20% of the components contain a 1,6 anhydro derivative on the reducing end of the chain, the range being between 15 and 25%.

The mass-average molecular mass ranges between 3,800 and 5,000 daltons with a characteristic value of about 4,500 daltons. The mass percentage of chains between 2,000 and 8,000 daltons ranges between 68.0 and 82.0 percent.

Molecular formula:



|   |                |   |                |
|---|----------------|---|----------------|
| R | X = 15 to 25 % |   | n = 0<br>to 20 |
|   | 100 - X        | H | n = 1<br>to 21 |

X = Percent of polysaccharide chain containing 1,6 anhydro derivative on the reducing end

Molecular mass: Relative molecular mass is about 4500 daltons (range: 3,800 - 5,000 daltons).

Physicochemical properties: Enoxaparin sodium is a fine white to almost white powder. Enoxaparin sodium is soluble in water, but practically insoluble in ethanol and chloroform. Aqueous solutions of enoxaparin sodium (10% aqueous solution) have a pH between 6.2 to 7.7.

## 14 CLINICAL TRIALS

### 14.1 Trial Design and Study Demographics

Clinical studies conducted to support similarity between REDESCA (enoxaparin sodium) and the reference biologic drug included:

- A comparative pharmacodynamic (PD) study performed in healthy volunteers (Study SPh/01/2013).

An overview of the study design and demographic characteristics of patients enrolled in the clinical study is presented in Table 11.

**Table 11 - Summary of patient demographics for clinical trials**

| Study       | Trial design                                                               | Dosage, route of administration and duration                                                                                                                                                                                                                                         | Study subjects (n)                                  | Mean age (Range)   | Sex                              |
|-------------|----------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|--------------------|----------------------------------|
| SPh/01/2013 | Randomised, open-label, single-dose, 2-way cross-over comparative PD study | REDESCA:<br>40 mg/0.4 ml (100 mg/mL), SC injection, in pre-filled syringes (single dose)<br>or<br>Clexane (EU):<br>40 mg/0.4 ml (100 mg/mL), SC injection, in pre-filled syringes (single dose) in each of the 2 treatment periods, separated by at least a washout period of 8 days | N= 20<br>Caucasian healthy male and female subjects | 28.8 years (19-47) | Male:<br>n=14<br>Female:<br>n= 6 |

Abbreviations: N= number of subjects

Study SPh/01/2013 was a randomised, open-label, single-dose, 2-way cross-over comparative pharmacodynamic (PD) study. The study evaluated 20 healthy subjects.

### 14.2 Study Results

*See 14.3 Comparative Bioavailability Studies*

### 14.3 Comparative Bioavailability Studies

#### 14.3.1.1 Pharmacodynamics

Study SPh/01/2013 was conducted with REDESCA and Clexane (sourced from the European Union), as a suitable proxy for the Canadian reference biologic Lovenox from Sanofi-Aventis Canada Inc.

This study was a randomised, open-label, single-dose, 2-way cross-over comparative pharmacodynamic (PD) study in 20 healthy volunteers to evaluate the PD comparability of REDESCA and Clexane (EU). Fasted subjects were exposed to a single subcutaneous dose of 100 mg/mL REDESCA (40 mg/0.4 mL) and Clexane (EU) (40 mg/0.4 mL). An 8-day washout separated doses. The main objective of the study was to assess to the pharmacodynamic (PD) comparability of REDESCA to the reference biologic drug. The primary PD parameters evaluated were maximum activity ( $A_{max}$ ) and area under the concentration effect curve from time 0 to the last measured activity ( $AUEC_{0-T}$ ) of anti-FXa and anti-FIIa activity.

The results of the primary PD comparisons are shown in Tables 12 and 13 below.

**Table 12 - Study SPH/01/2013 – Statistical Analysis of Primary PD Parameters**

| <b>Anti-FXa activity</b><br><b>(1 x 40 mg [100 mg/mL SC])</b><br><b>From measured data</b><br><br><b>Geometric Mean</b><br><b>Arithmetic Mean (CV %)</b> |                         |                              |                                   |                                            |
|----------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|------------------------------|-----------------------------------|--------------------------------------------|
| <b>Parameter</b>                                                                                                                                         | <b>Test<sup>§</sup></b> | <b>Reference<sup>†</sup></b> | <b>% Ratio of Geometric Means</b> | <b>95% Confidence Interval<sup>¶</sup></b> |
| $AUEC_{0-T}$<br>(h*IU/mL)                                                                                                                                | 3.9<br>4.0 (22.6)       | 3.7<br>3.8 (25.4)            | 105.7                             | 97.1- 115.1                                |
| $A_{MAX}$<br>(IU/mL)                                                                                                                                     | 0.5<br>0.5 (16.5)       | 0.5<br>0.5 (19.4)            | 104.8                             | 99.5- 110.4                                |
| $T_{MAX}$ (h) <sup>a</sup>                                                                                                                               | 3.2 (23.9)              | 3.0 (17.3)                   |                                   |                                            |

<sup>§</sup> REDESCA (enoxaparin sodium injection) by Shenzhen Techdow Pharmaceutical Co., Ltd, China.

<sup>†</sup> Clexane (EU) (enoxaparin sodium injection) by Sanofi-Aventis (as a suitable proxy for the reference biologic drug, Lovenox from Sanofi-Aventis Canada Inc.)

Abbreviations: CV= coefficient of variation;  $AUC_{0-t}$ = Area under the concentration time curve from time 0 until the last measurable concentration or last sampling time t, whichever occurs first;  $A_{max}$ = Maximum activity;  $T_{max}$  = time to achieve the maximum plasma concentration.

<sup>a</sup> Arithmetic mean (%CV).

<sup>¶</sup> Acceptance Interval was 80.0% to 125.0%

**Table 13 - Study SPH/01/2013 – Statistical Analysis of Primary PD Parameters**

| <b>Anti-FIIa activity</b><br><b>(1 x 40 mg [100 mg/mL SC])</b><br><b>From measured data</b><br><br><b>Geometric Mean</b><br><b>Arithmetic Mean (CV %)</b> |                         |                              |                                   |                                            |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|------------------------------|-----------------------------------|--------------------------------------------|
| <b>Parameter</b>                                                                                                                                          | <b>Test<sup>§</sup></b> | <b>Reference<sup>†</sup></b> | <b>% Ratio of Geometric Means</b> | <b>95% Confidence Interval<sup>¶</sup></b> |
| AUEC <sub>0-T</sub><br>(h*IU/mL)                                                                                                                          | 0.2<br>0.2 (23.6)       | 0.2<br>0.2 (39.0)            | 103.6                             | 90.3-118.8                                 |
| A <sub>MAX</sub><br>(IU/mL)                                                                                                                               | 0.1<br>0.1 (16.3)       | 0.1<br>0.1 (17.6)            | 102.2                             | 96.8-108.0                                 |
| T <sub>MAX</sub> (h) <sup>a</sup>                                                                                                                         | 3.2 (23.9)              | 3.0 (17.3)                   |                                   |                                            |

<sup>§</sup> REDESCA (enoxaparin sodium injection) by Shenzhen Techdow Pharmaceutical Co., Ltd, China.

<sup>†</sup> Clexane (EU) (enoxaparin sodium injection) by Sanofi-Aventis (as a suitable proxy for the reference biologic drug, Lovenox from Sanofi-Aventis Canada Inc.)

Abbreviations: CV= coefficient of variation; AUC<sub>0-t</sub>= Area under the concentration time curve from time 0 until the last measurable concentration or last sampling time t, whichever occurs first; A<sub>max</sub>= Maximum activity; T<sub>max</sub> = time to achieve the maximum plasma concentration.

<sup>a</sup> Arithmetic mean (%CV).

<sup>¶</sup> Acceptance Interval was 80.0% to 125.0%

#### **14.5 Clinical Trials - Reference Biologic Drug**

##### **Prophylaxis of venous thromboembolic disease following hip or knee surgery**

###### Study demographics and trial design [CPK 0884 P20, CPK 0387/PK523, CPK 0688/ PK527]

The safety and efficacy of enoxaparin sodium in preventing deep vein thrombosis (DVT) following hip or knee surgery has been evaluated in three large pivotal trials involving 896 patients over 40 years of age. The mean age was 67 years, with 40.2% men and 56.5% women. all studies were conducted as multi-centre, controlled, double-blind comparison of enoxaparin sodium with placebo or with calcium heparin in patients undergoing orthopedic surgery of the hip or knee. Treatment with enoxaparin sodium or the selected drug standard was initiated the day after or second day after surgery, provided hemostasis was established, and continued for 14 days or until discharge if sooner. All three studies shared the same objectives, criteria of evaluation and procedures.

**Table 14 - Summary of patient demographics in clinical trials for prophylaxis of venous thromboembolic disease following hip or knee surgery**

| Study #               | Trial Design                                                                                                                                             | Dosage, route of administration and duration                                                                                                              | Study subjects (n=number)    | Mean age (Range)                                      | Gender (M/F) |
|-----------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|-------------------------------------------------------|--------------|
| CPK 0884 P20 (Hip)    | Randomized, double-blind, parallel group,<br><br>To compare enoxaparin with placebo in prevention of DVT in patients undergoing total hip replacement    | <b>Enoxaparin</b><br>30 mg SC injection twice daily<br>or<br><b>Placebo</b><br>SC injection twice daily<br>Duration: up to 14 days                        | Total = 100<br>50<br><br>50  | 67.1 years (41-84)                                    | 45%/55%      |
| CPK 0387/PK523 (Hip)  | Randomized, double-blind, parallel group,<br>To compare enoxaparin with calcium heparin in prevention of DVT in patients undergoing elective hip surgery | <b>Enoxaparin</b><br>30 mg SC injection twice daily<br>or<br><b>Calcium heparin</b><br>7500 units SC injection twice daily<br><br>Duration: up to 14 days | Total: 665<br>333<br><br>332 | 67 years (66.2 ± 10.39)<br><br>67 years (66.8 ± 9.09) | 45.8%/ 54.2% |
| CPK 0688/PK527 (Knee) | Randomized, double-blind, parallel group,<br>To compare enoxaparin with placebo in prevention of DVT in patients undergoing major knee surgery           | <b>Enoxaparin</b><br>30 mg SC injection twice daily<br>or<br><b>Placebo</b><br>SC injection twice daily<br>Duration: up to 14 days                        | Total: 131<br>66<br><br>65   | 68.1 (42-85)                                          | 29.7%/60.3%  |

**Study results**

The primary aim of each study was to determine the efficacy and safety of enoxaparin sodium in the prevention of thromboembolism. Efficacy assessments were based on venography, <sup>125</sup>I-fibrinogen scanning of the lower limbs and impedance plethysmography (IPG). The efficacy data are provided below.

**Table 15 - Incidence of DVT in patients treated with enoxaparin or placebo, following hip or knee surgery**

| Study              | Incidence of DVT  |                   |                   | p-value  |
|--------------------|-------------------|-------------------|-------------------|----------|
|                    | LOVENOX group (%) | Placebo group (%) | heparin group (%) |          |
| CPK 0884 P20 (Hip) | 10                | 46                | –                 | 0.0002   |
| CPK 0387 (Hip)     | 17                | –                 | 19                | 0.5317   |
| CPK 0688 (Knee)    | 19.7              | 60.0              | –                 | < 0.0001 |

In patients undergoing total hip replacement (study CPK 0884), postoperative treatment with LOVENOX 30 mg s.c. twice daily statistically significantly reduced the incidence of DVT compared to placebo group (10% vs 46% respectively,  $p = 0.0002$ ). The odds ratio was 8.34 (95% CI = [2.72, 25.56],  $p = 0.0002$ ).

In patients undergoing elective hip surgery (study CPK0387), the incidence rate of DVT in the LOVENOX group was lower than in the calcium heparin group (17% vs 19% respectively), although the comparison between these groups was not statistically significant. LOVENOX 30 mg s.c. twice daily was shown to be at least as efficacious as calcium heparin 7500 units twice daily.

In patients undergoing major knee surgery (study CPK 0688) LOVENOX 30 mg twice daily significantly reduced the incidence rate of VTE disease relative to placebo (60% vs 19.7% respectively,  $p < 0.0001$ ). The estimated odds for development of VTE disease in the placebo group was 7.5 times higher than for the LOVENOX group (95% CI = [3.13 – 17.74]).

### **Extended Prophylaxis of DVT Following Hip Replacement Surgery**

#### Study demographics and trial design [Study 307]

In the open label phase of the multicentre study 307, patients undergoing elective primary hip replacement surgery received LOVENOX 30 mg SC twice daily for 7 to 10 days, initiated within 12 to 24 hours post surgery. Patients who did not require re-operation, had received appropriate LOVENOX dosing during the open-label phase, did not receive prohibited concomitant medications and had not developed DVT or PE, or experienced a major hemorrhage during the hospitalization were entered into the double-blind treatment phase. In the double-blind phase, 435 patients with unilateral primary hip replacements, revision, or previous joint replacements were randomized to a post discharge long-term regimen of LOVENOX 40 mg (n=224) q.d. SC or matching placebo (n=211) until a total of 28 days of therapy was administered (mean treatment duration 19 days). Patients ranged in age from 26 to 88 years (mean age 63.4 years) in the placebo group and from 28 to 90 years (mean age 64.4 years) in the LOVENOX group. The majority of patients were Caucasians with 49.9% men and 50.1% women. The primary endpoint of this study was the incidence of venous thromboembolism (VTE) during the double-blind treatment period. VTE constituted a treatment failure.

**Table 16 - Summary of patient demographics in clinical trials for extended prophylaxis of venous thromboembolic disease following hip surgery**

| Study #   | Trial Design                                                                                                                                                                                                                                                                                                          | Dosage, route of administration and duration                                                                                                                                                                                                                                                                                                                | Study subjects (n=number)                                                                                                             | Mean age (Range)                                                                                                             | Gender (M/F) |
|-----------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------|--------------|
| 307 (Hip) | Randomised, double-blind, parallel group, placebo-controlled, multicentre study<br><br>To evaluate the efficacy and safety of a prolonged post-hospital regimen of enoxaparin compared to placebo for the prevention of venous thromboembolic disease in patients undergoing elective, primary total hip replacement. | <b>Open label phase</b><br><b>Enoxaparin</b><br>30 mg SC b.i.d. initiated within 12 to 24 hours post surgery<br><b>Duration:</b> for 7 to 10 days.<br><br><b>Double-blind phase</b><br><br><b>Enoxaparin</b><br>40 mg q.d. SC or<br><br><b>Placebo</b><br>q.d. SC<br><b>Duration:</b> until a total of 28 days of therapy was administered (mean: 19 days). | Total = 475<br><br><br><br><br><br><br><br><br><br><br>Total = 435 (randomized)<br>224<br><br><br><br><br><br><br><br><br><br><br>211 | <br><br><br><br><br><br><br><br><br><br><br>64.4 years (28-90)<br><br><br><br><br><br><br><br><br><br><br>63.4 years (26-88) | 49.9%/50.1%  |

**Study results**

Extended prophylaxis with LOVENOX 40 mg q.d. SC resulted in statistically and clinically significant reductions in the incidence rates of VTE as compared to placebo treatment. PE was not observed in the LOVENOX treatment group but 1 patient in the placebo treatment group experienced both DVT and PE. An evaluation of the anatomic site of DVTs indicated a clinically and statistically significant reduction of patients who experienced proximal or proximal and distal DVTs. The effect was slightly less pronounced in patients with only distal DVT but remained clinically apparent.

**Table 17 - Efficacy of LOVENOX 40 mg q.d. SC in Extended Prophylaxis of DVT Following Hip Replacement Surgery\***

| Endpoints                            | Dosing Regimen              |                       | p-value |
|--------------------------------------|-----------------------------|-----------------------|---------|
|                                      | LOVENOX 40 mg q.d. SC n (%) | placebo q.d. SC n (%) |         |
| All Treated Hip Replacement Patients | 224                         | 211                   |         |
| All Failures                         | 18 (8.0)                    | 49 (23.2)             | < 0.001 |
| DVT location                         |                             |                       |         |
| at least proximal†                   | 6 (2.7)                     | 27 (12.8)             | < 0.001 |
| proximal                             | 4 (1.8)                     | 14 (6.6)              |         |
| Distal                               | 12 (5.4)                    | 22 (10.4)             |         |
| Proximal + distal                    | 2 (0.9)                     | 13 (6.2)              |         |
| DVT & PE                             | 0 (0.0%)                    | 1 (0.5%)              |         |

\* Multicentre study

† Includes patients with proximal DVT and those with both proximal and distal DVT

### Intraabdominal surgery

Two multicenter Phase III clinical trials (PK567 and PK568) were conducted in order to evaluate the efficacy and safety of LOVENOX in the prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE) in a total of 2462 patients undergoing colorectal and elective curative cancer surgery. Both studies were double blind and used standard heparin 5000 units subcutaneously every 8 hours as control; the study medication was initiated 2 hours preoperatively and continued for 6 to 12 days.

#### Study demographics and trial design [PK567]

Abdominal surgery patients at risk include those who are over 40 years of age, obese, undergoing surgery under general anesthesia lasting longer than 30 minutes or who have additional risk factors such as malignancy or a history of deep vein thrombosis or pulmonary embolism.

In a double-blind, parallel group study of patients undergoing elective cancer surgery of the gastrointestinal, urological, or gynecological tract, a total of 1116 patients were enrolled in the study, and 1115 patients were treated. Patients ranged in age from 32 to 97 years (mean age 67.1 years) with 52.7% men and 47.3% women. Patients were 98% Caucasian, 1.1% Black, 0.4% Oriental, and 0.4% others.

**Table 18 - Summary of patient demographics in clinical trial PK567 for the prophylaxis of deep vein thrombosis following abdominal surgery**

| Study # | Trial Design                                                                                                                                                                                                      | Dosage, route of administration and duration                                       | Study subjects (n=number) | Mean age (Range) | Gender (M/F) |
|---------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|---------------------------|------------------|--------------|
| PK567   | Multicentre, randomized, double-blind, heparin-controlled<br>To compare the safety and efficacy of enoxaparin with unfractionated heparin for prevention of DVT in patients after planned elective cancer surgery | <b>Enoxaparin</b><br>40 mg SC injection once daily*                                | Total: 1115               | 67.1<br>(32-97)  | 52.7%/47.3%  |
|         |                                                                                                                                                                                                                   | <b>HEPARIN</b><br>5000 units SC injection three times daily                        | 555                       |                  |              |
|         |                                                                                                                                                                                                                   | Duration: 6 to 12 days<br>median duration:<br>enoxaparin 9 days,<br>heparin 8 days | 560                       |                  |              |

\* In addition, the patients from enoxaparin group received 2 placebo injections

#### Study results

The primary efficacy variable was the incidence rate of VTE in all treated population. The aim of the study was to demonstrate that LOVENOX was at least as effective as heparin in prevention of DVT in abdominal surgery patients. The efficacy data are provided below.

**Table 19 - Efficacy of LOVENOX injection in the prophylaxis of deep vein thrombosis following abdominal surgery**

| Endpoints                              | Dosing Regimen                               |                                    |
|----------------------------------------|----------------------------------------------|------------------------------------|
|                                        | LOVENOX<br>40 mg q.d. SC<br>n (%)            | Heparin<br>5000 U q8 h SC<br>n (%) |
| All Treated Abdominal Surgery Patients | 555 (100)                                    | 560 (100)                          |
| Treatment failures                     |                                              |                                    |
| Total VTE <sup>1</sup> (%)             | 56 (10.1)<br>(95% CI <sup>2</sup> : 8 to 13) | 63 (11.3)<br>(95% CI: 9 to 14)     |
| DVT Only (%)                           | 54 (9.7)<br>(95% CI: 7 to 12)                | 61 (10.9)<br>(95% CI: 8 to 13)     |

<sup>1</sup> VTE = Venous thromboembolic events which included DVT, PE, and death considered to be thromboembolic in origin. The observed difference between the heparin and the enoxaparin group was 1.16% [90% CI = -4.20%; 1.88%]

<sup>2</sup> CI = Confidence Interval

LOVENOX injection 40 mg SC, administered once a day, beginning 2 hours prior to surgery and continuing for a maximum of 12 days after elective cancer surgery, was found to be as effective as heparin 5000 units every 8 hours s.c. in reducing the risk of deep vein thrombosis (DVT).

#### Study demographics and trial design [PK568]

In a second double-blind, parallel group study, LOVENOX injection 40 mg s.c. once a day was compared to heparin 5000 units every 8 hours s.c. in patients undergoing colorectal surgery (one third with cancer). A total of 1347 patients were randomized in the study and all patients were treated. Patients ranged in age from 18 to 92 years (mean age 50.1 years) with 54.2% men and 45.8% women.

**Table 20 - Summary of patient demographics in clinical trial PK568 for the prophylaxis of deep vein thrombosis following colorectal surgery**

| Study # | Trial Design                                                                                                                                                                    | Dosage, route of administration and duration                                                                                                                                 | Study subjects (n=number)         | Mean age (Range)  | Gender (M/F) |
|---------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|-------------------|--------------|
| PK568   | Multicentre, randomized, double-blind<br><br>To compare the efficacy and safety enoxaparin with calcium heparin for prevention of DVT in patients undergoing colorectal surgery | <b>Enoxaparin</b><br>40 mg SC injection once daily*<br><br><b>Heparin</b><br>5000 units SC injection, three times daily<br><br>Duration: 7-10 days<br><br>Follow-up: 6 weeks | Total: 1347<br><br>673<br><br>674 | 50.1<br>(18 - 92) | 54.2%/45.8%  |

\* In addition, the patients from enoxaparin group received 2 placebo injections

#### Study results

Treatment was initiated approximately 2 hours prior to surgery and continued for approximately 7 to 10 days after surgery. The primary efficacy variable was the incidence rate of VTE in the all-treated population. The primary objective of the study was to demonstrate that LOVENOX was at least as effective as heparin in preventing of DVT. The efficacy data are provided below.

**Table 21 - Efficacy of LOVENOX injection in the prophylaxis of deep vein thrombosis following colorectal surgery**

| Endpoints                              | Dosing Regimen                             |                                   |
|----------------------------------------|--------------------------------------------|-----------------------------------|
|                                        | LOVENOX<br>40 mg q.d. SC<br>n (%)          | Heparin<br>5000 U q8h SC<br>n (%) |
| All Treated Abdominal Surgery Patients | 673 (100)                                  | 674 (100)                         |
| Treatment failures                     |                                            |                                   |
| Total VTE <sup>1</sup> (%)             | 48 (7.1)<br>(95% CI <sup>2</sup> : 5 to 9) | 45 (6.7)<br>(95% CI: 5 to 9)      |
| DVT Only (%)                           | 47 (7.0)<br>(95% CI: 5 to 9)               | 44 (6.5)<br>(95% CI: 5 to 8)      |

<sup>1</sup> VTE = Venous thromboembolic events which included DVT, PE, and death considered to be thromboembolic in origin. The observed difference between the heparin and the enoxaparin group was 0.46% [95% CI = -2.25%; 3.16%]

<sup>2</sup> CI = Confidence Interval

In patients undergoing colorectal surgery treated for a maximum of 10 days, LOVENOX 40 mg once daily was found to be as effective as heparin 5000 units three times daily in the prevention of VTE disease.

#### **Prophylaxis of Venous Thromboembolism (VTE) In Medical Patients with Severely Restricted Mobility During Acute Illness**

##### Study demographics and trial design [MEDENOX (ENX395006)]

In a double blind multicenter, parallel group study, LOVENOX injection 20 mg or 40 mg once a day s.c. was compared to placebo in the prophylaxis of VTE in medical patients with severely restricted mobility during acute illness. This study included patients with heart failure (NYHA Class III or IV); acute respiratory failure or complicated chronic respiratory insufficiency (not requiring ventilatory support); acute infection (excluding septic shock); or acute rheumatic disorder [acute lumbar or sciatic pain, vertebral compression (due to osteoporosis or tumor), acute arthritic episodes of the lower extremities]. A total of 1102 patients were enrolled in the study, and 1073 patients were treated. A number of 866 patients were assessed for the incidence of venous thromboembolism. Patients ranged in age from 41 to 97 years (mean age 73.55 years) with 50.35% men and 49.65% women. Treatment continued for a maximum of 14 days (median duration 7 days), and patients were followed-up at day 90.

**Table 22 – Summary of patient demographics in clinical trial for the prophylaxis of deep vein thrombosis in medical patients with severely restricted mobility during acute illness**

| Study #             | Trial design                                                                                                                                                                                            | Dosage, route of administration and duration                                                                 | Study subjects (n=number)                                                    | Mean age (range) | Gender (M/F)    |
|---------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------|------------------|-----------------|
| MEDENOX (ENX395006) | Multicenter, randomized, double-blind, parallel group<br><br>To evaluate the safety and efficacy of two doses of enoxaparin for prevention of VTE in hospitalized patient with acute medical disorders. | 40 mg or 20 mg* enoxaparin or placebo, SC, once daily.<br><br>Duration: 6-14 days<br><br>Follow-up: 3 months | Total : 866<br><br>Enoxaparin<br>20 mg : 287<br>40 mg : 291<br>Placebo : 288 | 73,55 (41 - 97)  | 49,65 %/50,35 % |

\* There were no differences between LOVENOX 20 mg and the placebo groups. LOVENOX 20 mg is not an approved dose in Canada.

#### Study results

The primary outcome was venous thromboembolism between days 1 and 14, defined as deep vein thrombosis detected by bilateral venography (or duplex ultrasonography) between days 6 and 14 (or earlier if clinically indicated) or documented pulmonary embolism. The duration of follow-up was 3 months. The efficacy data are provided below.

**Table 23 – Efficacy of LOVENOX injection in the prophylaxis of deep vein thrombosis in medical patients with severely restricted mobility during acute illness**

| Endpoints                                             | Dosing Regimen                    |                  |
|-------------------------------------------------------|-----------------------------------|------------------|
|                                                       | LOVENOX<br>40 mg q.d. SC<br>n (%) | Placebo<br>n (%) |
| Patients randomized and assessed for primary efficacy | 291 (100)                         | 288 (100)        |
| Treatment Failure <sup>1</sup>                        |                                   |                  |
| Total VTE <sup>2</sup> (%)                            | 16 (5,5)                          | 43 (14,9)        |
| Total DVT (%)                                         | 16 (5,5)                          | 40 (13,9)        |
| Proximal DVT (%)                                      | 5 (1,7)                           | 14 (4,9)         |

<sup>1</sup> Treatment failures during therapy, between Days 1 and 14

<sup>2</sup> VTE = Venous thromboembolic events which included DVT, PE, and death considered to be thromboembolic in origin

When given at a dose of 40 mg once a day s.c., LOVENOX injection significantly reduced the incidence of DVT as compared to placebo. The relative risk reduction for total VTE events was 63% (95% CI = [37%; 78%],  $p = 0.0002$ ). At approximately 3 months following enrollment, the incidence of venous thromboembolism remained significantly lower in the LOVENOX injection 40 mg treatment group (19/272, 6.98%) versus the placebo treatment group (45/263, 17.11%), with a relative risk of 0.41 (95% CI between 0.25 and 0.68,  $p = 0.0003$ ).

### Treatment of Deep Vein Thrombosis (DVT) with or without Pulmonary Embolism (PE)

The safety and efficacy of enoxaparin in the treatment of DVT with or without PE has been evaluated in 2 clinical trials (PK529 and CPK2091) involving 1401 patients.

#### Study demographics and trial design [PK529]

In a multicenter, parallel group study, 900 patients with acute lower extremity DVT with or without PE were randomized to an inpatient (hospital) treatment of either (i) LOVENOX injection 1.5 mg/kg once a day SC, (ii) LOVENOX injection 1 mg/kg every 12 hours SC, or (iii) heparin IV bolus (5000 units) followed by a continuous infusion (administered to achieve an aPTT of 55 to 85 seconds). A total of 900 patients were randomized in the study and all patients were treated. Patients ranged in age from 18 to 92 years (mean age 60.7 years) with 54.7% men and 45.3% women. All patients also received warfarin sodium (dose adjusted according to PT to achieve an International Normalization Ratio [INR] of 2.0 to 3.0), commencing within 72 hours of initiation of LOVENOX injection or standard heparin therapy, and continuing for 90 days. LOVENOX injection or standard heparin therapy was administered for a minimum of 5 days and until the targeted warfarin sodium INR was achieved.

**Table 24 - Summary of patient demographics in clinical trial comparing the efficacy of LOVENOX with heparin for treatment of venous thromboembolic disease**

| Study # | Trial Design                                                                                                                                                                                     | Dosage, route of administration and duration                                                                                                                                               | Study subjects (n=number) | Mean age (Range)  | Gender (M/F) |
|---------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|-------------------|--------------|
| PK529   | Multicenter, randomized, controlled, partially blind, parallel group<br>To compare the efficacy and safety of enoxaparin with heparin in the treatment of DVT with or without pulmonary embolism | <b>Enoxaparin</b><br>1 mg/kg s.c. twice daily<br>or<br>1.5 mg/kg once daily                                                                                                                | Total=900                 | 60.7<br>(18 - 92) | 54.7%/45.3%  |
|         |                                                                                                                                                                                                  |                                                                                                                                                                                            | 312                       |                   |              |
|         |                                                                                                                                                                                                  |                                                                                                                                                                                            | 298                       |                   |              |
|         |                                                                                                                                                                                                  | <b>Heparin</b><br>IV bolus (5000 U)<br>followed by a continuous infusion<br>Duration: minimum of 5 days and until the targeted warfarin sodium INR was achieved<br>Median duration: 7 days | 290                       |                   |              |

\* All patients also received warfarin sodium

#### Study results

The primary objective of this study was to demonstrate that LOVENOX was as effective as heparin in the heparin group and both the once and twice-daily LOVENOX treatment groups for the incidence of recurrent deep venous thrombosis or pulmonary embolism within 3 month of randomization in all treated patients. The efficacy data are provided below.

LOVENOX administered as a 1 mg/kg twice-daily regimen or a 1.5 mg/kg once-daily regimen was found to be as effective as the regimen of adjusted-dose, continuous infusion heparin therapy for the prevention of recurrent VTE disease in patients with acute deep vein thrombosis with or without pulmonary embolism.

**Table 25 - Efficacy of LOVENOX injection in treatment of deep vein thrombosis with or without pulmonary embolism**

| Endpoints                                                   | Dosing Regimen <sup>1</sup>  |                              |                                        |
|-------------------------------------------------------------|------------------------------|------------------------------|----------------------------------------|
|                                                             | LOVENOX<br>1.5 mg/kg q.d. SC | LOVENOX<br>1 mg/kg q 12 h SC | Heparin<br>aPTT adjusted<br>IV Therapy |
|                                                             | n (%)                        | n (%)                        | n (%)                                  |
| All Treated DVT Patients with or without PE Patient Outcome | 298 (100)                    | 312 (100)                    | 290 (100)                              |
| Total VTE <sup>2</sup> (%)                                  | 13 (4.4)                     | 9 (2.9) <sup>3</sup>         | 12 (4.1)                               |
| DVT Only (%)                                                | 11 (3.7)                     | 7 (2.2)                      | 8 (2.8)                                |
| Proximal DVT (%)                                            | 9 (3.0)                      | 6 (1.9)                      | 7 (2.4)                                |
| PE (%)                                                      | 2 (0.7)                      | 2 (0.6)                      | 4 (1.4)                                |

<sup>1</sup> All patients were also treated with warfarin sodium commencing within 72 hours of LOVENOX Injection or standard heparin therapy.

<sup>2</sup> VTE = venous thromboembolic event (DVT and/or PE).

<sup>3</sup> The 95% Confidence Intervals for the treatment differences for total VTE were:

LOVENOX Injection once a day versus heparin (-3.0 to 3.5)

LOVENOX Injection every 12 hours versus heparin (-4.2 to 1.7).

#### Study demographics and trial design [CPK2091]

Similarly, in a multicenter, open-label, parallel group study, patients with acute proximal DVT were randomized to LOVENOX injection or heparin. Patients who could not receive outpatient therapy were excluded from entering the study. Outpatient exclusion criteria included the following: inability to receive outpatient heparin therapy because of associated co-morbid conditions or potential for non-compliance and inability to attend follow-up visits as an outpatient because of geographic inaccessibility. Eligible patients could be treated in the hospital, but ONLY LOVENOX injection patients were permitted to go home on therapy (72%). A total of 501 patients were randomized in the study and all patients were treated. Patients ranged in age from 19 to 96 years (mean age 57.8 years) with 60.5% men and 39.5% women. Patients were randomized to either LOVENOX injection 1 mg/kg every 12 hours SC or heparin IV bolus (5000 units) followed by a continuous infusion administered to achieve an aPTT of 60 to 85 seconds (in-patient treatment). All patients also received warfarin sodium as described in the previous study. LOVENOX injection or standard heparin therapy was administered for a minimum of 5 days.

**Table 26 - Summary of patient demographics in CPK2091 clinical trial comparing the efficacy of LOVENOX with heparin for treatment of deep vein thrombosis**

| Study # | Trial Design                                                                                                                                                                                                                | Dosage, route of administration and duration                                          | Study subjects (n=number) | Mean age (Range) | Gender (M/F) |
|---------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------|---------------------------|------------------|--------------|
| CPK2091 | Multicenter, randomized, open label, parallel group<br>To compare the efficacy and safety of outpatient enoxaparin regimen with standard inpatient heparin regimen in reducing the risk of recurrent venous thromboembolism | <b>Enoxaparin</b><br>1mg/kg twice daily                                               | Total = 501<br><br>247    | 61<br>(19 - 96)  | 60.5%/39.5%  |
|         |                                                                                                                                                                                                                             | <b>Heparin</b><br>IV - bolus (5000 U)<br>followed by a continuous infusion of 20000 U | 254                       |                  |              |
|         |                                                                                                                                                                                                                             | Duration: 5 days                                                                      |                           |                  |              |

| Study # | Trial Design | Dosage, route of administration and duration                  | Study subjects (n=number) | Mean age (Range) | Gender (M/F) |
|---------|--------------|---------------------------------------------------------------|---------------------------|------------------|--------------|
|         |              | median duration for all groups: 6 days<br>Follow-up: 3 months |                           |                  |              |

\* All patients also received warfarin sodium

### Study results

The primary efficacy endpoint was the incidence of VTE disease in all-treated patients. The primary objective in patients with acute proximal DVT was to compare the efficacy and safety of outpatient anticoagulant regimen consisting of fixed-dose subcutaneous LOVENOX injection with a standard inpatient anticoagulant regimen consisting of unfractionated heparin administered by continuous intravenous infusion. The efficacy data are provided below.

**Table 27 - Efficacy of LOVENOX in treatment of deep vein thrombosis**

| Endpoints                  | Dosing Regimen <sup>1</sup>          |                  |
|----------------------------|--------------------------------------|------------------|
|                            | LOVENOX<br>1 mg/kg q 12h SC<br>n (%) | Placebo<br>n (%) |
| All Treated DVT Patients   | 247 (100)                            | 254 (100)        |
| Patient Outcome            |                                      |                  |
| Total VTE <sup>2</sup> (%) | 13 (5.3) <sup>3</sup>                | 17 (6.7)         |
| DVT (%)                    | 11 (4.5)                             | 14 (5.5)         |
| Proximal DVT (%)           | 10 (4.0)                             | 12 (4.7)         |
| PE (%)                     | 2 (0.8)                              | 3 (1.2)          |

<sup>1</sup> All patients were also treated with warfarin sodium commencing on the evening of the second day of Lovenox Injection or standard heparin therapy.

<sup>2</sup> VTE = Venous thromboembolic event (deep vein thrombosis (DVT) and/or pulmonary embolism (PE)).

<sup>3</sup> The 95% Confidence Intervals for the treatment difference for total VTE was Heparin vs Lovenox injection (-2.272, 5.58)

In patients with proximal DVT, LOVENOX injection given as a fixed dose of 1 mg/kg s.c. twice daily was found to be as effective as standard heparin therapy administered as a continuous i.v. infusion in reducing the risk of recurrent VTE.

### Prophylaxis of Ischemic Complications in Unstable Angina and Non-Q-Wave Myocardial Infarction

#### Study demographics and trial design [ESSENCE - RP54563q-303]

In a multicenter, double-blind, parallel group study, patients who recently experienced unstable angina or non-Q-wave myocardial infarction were randomized to either LOVENOX injection 1 mg/kg every 12 hours SC or heparin IV bolus (5000 units) followed by a continuous infusion (adjusted to achieve an aPTT of 55 to 85 seconds). A total of 3171 patients were enrolled in the study, and 3107 patients were treated. Patients ranged in age from 25-94 years (median age 63.7 years), with 33.6% of patients female and 66.4% male. Race was distributed as follows: 89.8% Caucasian, 4.8% Black, 2.0% Oriental, and 3.5% other. All patients were also treated with aspirin 100 to 325 mg per day. Treatment was initiated within 24 hours of the event and continued until clinical stabilization, revascularization procedures, or hospital discharge, with a maximal duration of 8 days of therapy.

**Table 28 - Summary of patient demographics for clinical trial of LOVENOX injection in the prophylaxis of ischemic complications in unstable angina and non-Q-wave myocardial infarction**

| Study #                                                                                                       | Trial Design                                                                                                                                                                         | Dosage, route of administration and duration                                                                                                                                                         | Study subjects (n=number)            | Mean age (Range) | Gender (M/F) |
|---------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|------------------|--------------|
| ESSENCE<br>(Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q wave Coronary Events)<br><br>RP54563q-303 | Multicenter, randomized, double-blind, placebo-controlled<br>To compare efficacy and safety of enoxaparin with heparin in preventing ischemic complications in patients with UA/NQMI | <b>Enoxaparin</b><br>1 mg/kg subcutaneously, twice daily<br><br><b>Heparin</b><br>IV- bolus (5000 U) followed by a continuous infusion<br><br>Duration: 48 h-8 days<br><br>Median duration: 2.6 days | Total = 3107<br><br>1578<br><br>1529 | 63.7<br>(25-94)  | 66.4%/33.6%  |

\* All patients were also treated with aspirin 100 to 325 mg per day

#### Study results

The primary efficacy parameter was the incidence of the composite triple endpoint of death, myocardial infarction (MI), and recurrent angina at day 14. The efficacy data are provided below.

**Table 29 - Efficacy of LOVENOX injection in the prophylaxis of ischemic complications in unstable angina and non-Q-wave myocardial infarction (combined endpoint of death, myocardial infarction, or recurrent angina)**

| Endpoints                                              | Dosing Regimen <sup>1</sup>                           |                                                 |               |         |
|--------------------------------------------------------|-------------------------------------------------------|-------------------------------------------------|---------------|---------|
|                                                        | LOVENOX <sup>3</sup><br>1 mg/kg q 12h SC<br><br>n (%) | Heparin<br>aPTT Adjusted<br>IV Therapy<br>n (%) | Reduction (%) | p-value |
| All Treated Unstable Angina and Non-Q-Wave MI Patients | 1578 (100)                                            | 1529 (100)                                      |               |         |
| Time point <sup>2</sup>                                |                                                       |                                                 |               |         |
| 48 hours                                               | 96 (6.1)                                              | 112 (7.3)                                       | 1.2           | 0.120   |
| 14 days                                                | 261 (16.5)                                            | 303 (19.8)                                      | 3.3           | 0.017   |

<sup>1</sup> All patients were also treated with aspirin 100 to 325 mg per day.

<sup>2</sup> Evaluation timepoints are after initiation of treatment. Therapy continued for up to 8 days (median duration of 2.6 days).

<sup>3</sup> No capping of dose based on patient weight

The combined incidence of the triple endpoint (death, MI, recurrent angina) was significantly lower for LOVENOX injection compared with heparin therapy at 14 days after initiation of treatment in all-treated patients (16.5% vs 19.8%,  $p = 0.017$ ). The lower incidence of the triple endpoint was sustained up to 30 days after initiation of treatment (19.8% in LOVENOX group vs 23.3% in heparin group,  $p = 0.016$ ). These results were observed in an analysis of both all-randomized and all-treated patients.

### Benefit of LOVENOX beyond 30 days post-treatment period, up to 1 year

The ESSENCE – 1 year follow-up study and TIMI 11B clinical trial evaluated the benefits of LOVENOX beyond 30 days post-treatment period up to 1 year.

#### Study demographics and trial design [ESSENCE – 1-year follow-up]

In order to determine whether or not the observed superiority of LOVENOX over heparin shown in the early phase of ESSENCE trial persisted during long-term follow-up, a one-year follow-up survey was undertaken in all patients enrolled in the ESSENCE study. The one-year follow-up period was defined as time of randomization through one-year assessment or last contact. A retrospective collection of data was organized 1 year after the end of the study, whereby each site was requested to contact by telephone all randomized patients, and to provide the appropriate documentation concerning the efficacy endpoints. Complete information from 2915 patients was finally available, and 2992 patients had information available on their vital status at one year. Patients not reported as dead after the research were still considered lost to follow-up for the purpose of the analysis.

**Table 30 - Summary of patient demographics for ESSENCE – 1-year follow-up clinical Trial**

| Study #                    | Trial Design                     | Dosage, route of administration and duration | Study subjects (n=number)                           | Mean age (Range) | Gender (M/F) |
|----------------------------|----------------------------------|----------------------------------------------|-----------------------------------------------------|------------------|--------------|
| ESSENCE – 1-year follow-up | Retrospective collection of data | See ESSENCE clinical trial                   | Total = 2915<br>enoxaparin : 1469<br>heparin : 1446 | 64<br>(25-94)    | 66.1/33.9%   |

#### Study results

For this study, the same composite triple end-point of death, MI or recurrent angina was used, and the time to first composite triple end-point was the primary outcome. The efficacy data are provided below.

**Table 31 - Summary of major event incidence from randomization to 1 year follow-up in the ESSENCE – 1-year follow-up study**

| Endpoints                      | Dosing Regimen <sup>1</sup> |                       |              |                     |
|--------------------------------|-----------------------------|-----------------------|--------------|---------------------|
|                                | LOVENOX<br>n (est. %)       | Heparin<br>n (est. %) | Hazard ratio | Log Rank<br>p-value |
| Number of patients             | 1607                        | 1564                  |              |                     |
| Triple endpoint                | 498 (32.0)                  | 543 (35.7)            | 0.87         | 0.0217              |
| Death (including resuscitated) | 94 (6.0)                    | 114 (7.5)             | 0.80         | 0.0995              |
| Myocardial infarction          | 106 (7.0)                   | 123 (8.2)             | 0.83         | 0.1613              |
| Recurrent angina               | 364 (25.7)                  | 417 (28.0)            | 0.90         | 0.1207              |

\* est.% = percentages obtained from Kaplan-Meier curves (estimated probabilities taking into account the patients lost to follow-up)

Incidences of the components of triple endpoints are not mutually exclusive.

Deaths include 31 (19 heparin, 12 enoxaparin) resuscitations through 12 months.

<sup>1</sup> No capping of dose based on patient weight.

The primary efficacy parameter was significantly lower in patients assigned to LOVENOX compared to heparin (32% vs 35.7% respectively,  $p = 0.0217$ ). The rates of cardiac catheterizations (55.8% vs 59.4%,  $p = 0.036$ ) as well as the rates of revascularizations (35.9% vs 41.2%,  $p = 0.002$ ) were significantly lower in the LOVENOX group than in the heparin group.

#### Study demographics and trial design [TIMI 11B]

Study TIMI 11B was a multicenter, randomized, double-blind, double-dummy, parallel group clinical trial designed to evaluate the efficacy and safety of uninterrupted subcutaneous treatment with LOVENOX vs heparin in patients with unstable angina/non-Q-wave myocardial infarction (UA/NQMI). The study

consisted of two phases of treatment: (1) an acute phase – in-hospital treatment of weight-based medication, and (2) a chronic phase, consisted of out-patient treatment with study medication, for 35 days, starting from hospital discharge or days 8, whichever came first. The medication consisted of heparin for  $\geq 3$  days followed by s.c placebo injections or continuous antithrombin therapy with LOVENOX during both the acute phase (30 mg iv bolus, followed by 1 mg/kg every 12 hours) and outpatient phase (40 – 60 mg every 12 hours). A total number of 3910 were randomized; 3874 patients were treated during the acute phase and 2364 during the chronic phase. Median age was 64.3 years (range 29-93 years) with 64.8% males and 35.2 % females.

**Table 32 - Summary of patient demographics for TIMI 11B clinical trial**

| Study #                                                                                                         | Trial Design                                                                                                                                                             | Dosage <sup>§</sup> , route of administration and duration                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Study subjects (n=number)                  | Mean age (Range)**                         | Gender** (M/F)                          |  |              |            |                                                                |             |                  |                                          |                            |                  |          |                                  |                  |                   |                                          |  |  |  |              |                 |             |
|-----------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|--------------------------------------------|-----------------------------------------|--|--------------|------------|----------------------------------------------------------------|-------------|------------------|------------------------------------------|----------------------------|------------------|----------|----------------------------------|------------------|-------------------|------------------------------------------|--|--|--|--------------|-----------------|-------------|
| TIMI 11B<br>(Thrombolysis in Myocardial Infarction)                                                             | Multicenter, randomized, double-blind, double-dummy, parallel group<br>To assess the effect of enoxaparin compared to HEPARIN in the management of patients with UA/NQMI | <table><tr><td></td><td colspan="3">Acute Phase<br/>(Weight Adjusted treatment)</td></tr><tr><td></td><td>IV boluses</td><td>SC Injection</td><td>IV Infusion</td></tr><tr><td>Enoxaparin</td><td>Enoxaparin 30 mg<br/>Placebo 70 U/kg</td><td>Enoxaparin 1.0 mg/kg q 12h</td><td>Matching placebo</td></tr><tr><td>HEPARIN*</td><td>HEPARIN 70 U/kg<br/>Placebo 30 mg</td><td>Matching placebo</td><td>HEPARIN 15 U/kg/h</td></tr><tr><td colspan="4">*Adjusted to an PTT of 1.5-2.5 x control</td></tr></table> |                                            | Acute Phase<br>(Weight Adjusted treatment) |                                         |  |              | IV boluses | SC Injection                                                   | IV Infusion | Enoxaparin       | Enoxaparin 30 mg<br>Placebo 70 U/kg      | Enoxaparin 1.0 mg/kg q 12h | Matching placebo | HEPARIN* | HEPARIN 70 U/kg<br>Placebo 30 mg | Matching placebo | HEPARIN 15 U/kg/h | *Adjusted to an PTT of 1.5-2.5 x control |  |  |  | Total = 3874 | 64.3<br>(29-93) | 64.8%/35.2% |
|                                                                                                                 |                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Acute Phase<br>(Weight Adjusted treatment) |                                            |                                         |  |              |            |                                                                |             |                  |                                          |                            |                  |          |                                  |                  |                   |                                          |  |  |  |              |                 |             |
|                                                                                                                 |                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | IV boluses                                 | SC Injection                               | IV Infusion                             |  |              |            |                                                                |             |                  |                                          |                            |                  |          |                                  |                  |                   |                                          |  |  |  |              |                 |             |
|                                                                                                                 |                                                                                                                                                                          | Enoxaparin                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Enoxaparin 30 mg<br>Placebo 70 U/kg        | Enoxaparin 1.0 mg/kg q 12h                 | Matching placebo                        |  |              |            |                                                                |             |                  |                                          |                            |                  |          |                                  |                  |                   |                                          |  |  |  |              |                 |             |
|                                                                                                                 |                                                                                                                                                                          | HEPARIN*                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | HEPARIN 70 U/kg<br>Placebo 30 mg           | Matching placebo                           | HEPARIN 15 U/kg/h                       |  |              |            |                                                                |             |                  |                                          |                            |                  |          |                                  |                  |                   |                                          |  |  |  |              |                 |             |
|                                                                                                                 |                                                                                                                                                                          | *Adjusted to an PTT of 1.5-2.5 x control                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                            |                                            |                                         |  |              |            |                                                                |             |                  |                                          |                            |                  |          |                                  |                  |                   |                                          |  |  |  |              |                 |             |
|                                                                                                                 |                                                                                                                                                                          | Duration: until hospital discharge or day 8<br>Median duration:<br>enoxaparin: 4.63 days, heparin 3.02 days                                                                                                                                                                                                                                                                                                                                                                                                       |                                            | 1938                                       |                                         |  |              |            |                                                                |             |                  |                                          |                            |                  |          |                                  |                  |                   |                                          |  |  |  |              |                 |             |
|                                                                                                                 |                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                            | 1936                                       |                                         |  |              |            |                                                                |             |                  |                                          |                            |                  |          |                                  |                  |                   |                                          |  |  |  |              |                 |             |
|                                                                                                                 |                                                                                                                                                                          | <table><tr><td></td><td>Chronic Phase<br/>(Fixed-dose treatment)</td></tr><tr><td></td><td>SC injection</td></tr><tr><td>Enoxaparin</td><td>Enoxaparin<br/>≥ 65 kg – 60 mg q 12 h<br/>&lt; 65 kg – 40 mg q 12 h</td></tr><tr><td>HEPARIN*</td><td>Matching Placebo</td></tr><tr><td colspan="2">*Adjusted to an PTT of 1.5-2.5 x control</td></tr></table>                                                                                                                                                        |                                            |                                            | Chronic Phase<br>(Fixed-dose treatment) |  | SC injection | Enoxaparin | Enoxaparin<br>≥ 65 kg – 60 mg q 12 h<br>< 65 kg – 40 mg q 12 h | HEPARIN*    | Matching Placebo | *Adjusted to an PTT of 1.5-2.5 x control |                            | Total = 2364     |          |                                  |                  |                   |                                          |  |  |  |              |                 |             |
|                                                                                                                 |                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Chronic Phase<br>(Fixed-dose treatment)    |                                            |                                         |  |              |            |                                                                |             |                  |                                          |                            |                  |          |                                  |                  |                   |                                          |  |  |  |              |                 |             |
|                                                                                                                 | SC injection                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                            |                                            |                                         |  |              |            |                                                                |             |                  |                                          |                            |                  |          |                                  |                  |                   |                                          |  |  |  |              |                 |             |
| Enoxaparin                                                                                                      | Enoxaparin<br>≥ 65 kg – 60 mg q 12 h<br>< 65 kg – 40 mg q 12 h                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                            |                                            |                                         |  |              |            |                                                                |             |                  |                                          |                            |                  |          |                                  |                  |                   |                                          |  |  |  |              |                 |             |
| HEPARIN*                                                                                                        | Matching Placebo                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                            |                                            |                                         |  |              |            |                                                                |             |                  |                                          |                            |                  |          |                                  |                  |                   |                                          |  |  |  |              |                 |             |
| *Adjusted to an PTT of 1.5-2.5 x control                                                                        |                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                            |                                            |                                         |  |              |            |                                                                |             |                  |                                          |                            |                  |          |                                  |                  |                   |                                          |  |  |  |              |                 |             |
| Duration: 35 days<br>Median duration:<br>enoxaparin 34.4 days, heparin 34.5 days<br>Follow-up: 3 months, 1 year |                                                                                                                                                                          | 1179                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                            |                                            |                                         |  |              |            |                                                                |             |                  |                                          |                            |                  |          |                                  |                  |                   |                                          |  |  |  |              |                 |             |
|                                                                                                                 |                                                                                                                                                                          | 1185                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                            |                                            |                                         |  |              |            |                                                                |             |                  |                                          |                            |                  |          |                                  |                  |                   |                                          |  |  |  |              |                 |             |
|                                                                                                                 |                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                            |                                            |                                         |  |              |            |                                                                |             |                  |                                          |                            |                  |          |                                  |                  |                   |                                          |  |  |  |              |                 |             |
|                                                                                                                 |                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                            |                                            |                                         |  |              |            |                                                                |             |                  |                                          |                            |                  |          |                                  |                  |                   |                                          |  |  |  |              |                 |             |
|                                                                                                                 |                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                            |                                            |                                         |  |              |            |                                                                |             |                  |                                          |                            |                  |          |                                  |                  |                   |                                          |  |  |  |              |                 |             |
|                                                                                                                 |                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                            |                                            |                                         |  |              |            |                                                                |             |                  |                                          |                            |                  |          |                                  |                  |                   |                                          |  |  |  |              |                 |             |

§ Both treatment groups received 100-325 mg aspirin daily

\*\* All-randomized patients

### Study results

The primary study objective was to demonstrate that a strategy of uninterrupted aspirin and s.c. administration of weight-adjusted LOVENOX, followed by fixed-dose LOVENOX for up to 43 days was superior to a strategy of short-term heparin and aspirin for the prevention of death, nonfatal (re)infarction, and severe recurrent ischemia requiring urgent revascularization in patients with unstable angina and non-Q-wave myocardial infarction. The efficacy data are provided below.

**Table 33 - Summary of efficacy data of LOVENOX injection in patients with unstable angina and non-Q-wave myocardial infarction (TIMI 11B clinical trial)<sup>1</sup>**

| Endpoints                                            | LOVENOX<br>N=1953<br>n (%) | Heparin<br>N=1957<br>N (%) | Odds Ratio<br>(95% CI)         |
|------------------------------------------------------|----------------------------|----------------------------|--------------------------------|
| Triple endpoint                                      | 337 (17.3)                 | 385 (19.7)                 | 0.85 (0.72; 1.00) <sup>3</sup> |
| Death                                                | 75 (3.8)                   | 79 (4.0)                   | 0.96 (0.69; 1.33)              |
| Myocardial infarction                                | 107 (5.6)                  | 129 (6.6)                  | 0.82 (0.63; 1.07)              |
| Recurrent angina leading to urgent revascularization | 208 (10.7)                 | 247 (12.6)                 | 0.82 (0.67; 1.00)              |

<sup>1</sup> All-randomized population<sup>2</sup> Through day 43<sup>3</sup>  $p = 0.048$ <sup>4</sup> No capping of dose based on patient weight**Table 34 - Incidence of triple endpoint at different timepoints in patients with unstable angina and non-Q-wave myocardial infarction (TIMI 11B clinical trial)**

| Timepoints | LOVENOX<br>N=1953<br>n (%) | Heparin<br>N=1957<br>n (%) | Odds ratio | 95% CI for<br>odds ratio | p-value |
|------------|----------------------------|----------------------------|------------|--------------------------|---------|
| 48 hours   | 108 (5.5)                  | 142 (7.3)                  | 0.75       | (0.58, 0.97)             | 0.026   |
| Day 8      | 242 (12.4)                 | 284 (14.5)                 | 0.83       | (0.69, 1.00)             | 0.048   |
| Day 14     | 277 (14.2)                 | 326 (16.7)                 | 0.82       | (0.69, 0.98)             | 0.029   |
| Day 43     | 337 (17.3)                 | 385 (19.7)                 | 0.85       | (0.72, 1.00)             | 0.048   |

At 43 days, the incidence of the triple endpoint (death, MI or severe recurrent ischemia requiring urgent revascularization) was lower with LOVENOX than with heparin (17.3% vs 19.7% respectively), representing a 12.3% relative risk reduction ( $p = 0.048$ ). A significant reduction in the incidence of triple endpoint was also consistently observed at 48 hours, 8 days and 14 days. The double endpoint (death or MI) was also consistently reduced at all timepoints, although the reduction did not achieve statistical significance.

### Treatment of acute ST-segment Elevation Myocardial Infarction (STEMI)

#### Study demographics and trial design [XRP4563B/3001 ExTRACT-TIMI 25]

In a multicenter, double-blind, double-dummy, parallel group study (XRP4563B/3001 ExTRACT-TIMI 25), patients with STEMI who were eligible to receive fibrinolytic therapy were randomized in a 1:1 ratio to receive either LOVENOX or unfractionated heparin. All patients were also treated with aspirin for a minimum of 30 days. Study medication was administered between 15 minutes before and 30 minutes after the initiation of fibrinolytic therapy. Unfractionated heparin was administered beginning with an IV bolus of 60 U/kg (maximum 4000 U) and followed with an infusion of 12 U/kg per hour (initial maximum 1000 U per hour) that was adjusted to maintain an aPTT of 1.5 to 2.0 times the control value. The IV infusion was to be given for at least 48 hours. The enoxaparin dosing strategy was adjusted according to the patient's age and renal function. For patients younger than 75 years of age, enoxaparin was given as a single 30-mg intravenous bolus plus a 1 mg/kg SC dose followed by an SC injection of 1.0 mg/kg every 12 hours. For patients at least 75 years of age, the IV bolus was not given and the SC dose was reduced to 0.75 mg/kg every 12 hours. For patients with severe renal insufficiency (estimated creatinine clearance of less than 30 ml per minute), the dose was to be modified to 1.0 mg per kilogram every 24 hours. The SC injections of enoxaparin were given until hospital discharge or for a maximum of eight days (whichever came first).

When percutaneous coronary intervention was performed during study medication period, patients were to receive antithrombotic support with blinded study drug. Therefore, for patients on enoxaparin, the PCI was to be performed on enoxaparin (no switch) using the regimen established in previous studies, *i.e.* no additional dosing, if the last SC administration given less than 8 hours before balloon inflation, IV bolus of 0.3 mg/kg enoxaparin-if the last SC administration given more than 8 hours before balloon inflation.

A total of 20,506 patients were enrolled in the study, and 20,479 patients were included in the ITT population. Patients ranged in age from 20-99 years (mean age 59.8 years), with 23.5 % of patients female and 76.5 % male. Race was distributed as follows: 87.2% Caucasian, 0.2% Black, 9.8% Asian, and 2.8 % other. A fibrinolytic agent was administered to all but 4 patients, with 79.8% receiving a fibrin-specific agent and 20.2% receiving streptokinase. 4,716 patients underwent percutaneous coronary interventions.

**Table 35 - Summary of patient demographics for the treatment of acute ST-segment Elevation Myocardial Infarction (STEMI)**

| Study #                             | Trial Design                                                                                                                                                                                                 | Dosage, route of administration and duration                                                                                                                                                                   | Study subjects (n=number) | Mean age (Range) | Gender (M/F) |
|-------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------|--------------|
| XRP4563B/3001<br>ExTRACT-TIMI<br>25 | Randomized, double-blind, double-dummy, parallel group, multinational study.<br>To evaluate the efficacy and safety of enoxaparin versus HEPARIN in patients with acute STEMI receiving fibrinolytic therapy | <b>Enoxaparin</b>                                                                                                                                                                                              | Total = 20 479            |                  |              |
|                                     |                                                                                                                                                                                                              | <b>Patients &lt;75 Years of Age</b><br>Initial 30 mg iv bolus, followed by 1.0 mg/kg SC injection (maximum 100 mg/injection for first 2 injections) Q12h (first SC dose to be given within 15 min of iv bolus) | 10 256                    | 59.8<br>(20- 99) | 7841/2415    |
|                                     |                                                                                                                                                                                                              | <b>Patients ≥75 Years of Age</b><br>(No bolus)<br>0.75 mg/kg SC injection (maximum 75 mg/injection for first 2 injections) Q12h                                                                                |                           |                  |              |
|                                     |                                                                                                                                                                                                              | <b>Patients with CrCl &lt;30 mL/min<sup>ab</sup></b><br>Initial 30 mg iv bolus, followed by 1.0 mg/kg SC injection Q24h (first SC dose to be given within 15 min of iv bolus)                                  | 10 223                    | 59.9<br>(20- 98) | 7855/2368    |
|                                     |                                                                                                                                                                                                              | Duration of treatment: 8 days                                                                                                                                                                                  |                           |                  |              |

| Study # | Trial Design | Dosage, route of administration and duration                                                                                                                                                                                                                                            | Study subjects (n=number) | Mean age (Range) | Gender (M/F) |
|---------|--------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|------------------|--------------|
|         |              | <b>HEPARIN</b><br><br><b>All patients:</b><br>Initial 60 U/kg iv bolus (maximum 4000 U), followed by continuous infusion (initially at 12 U/kg per h) maximum 1000 U/h with adjustment as per aPTT (start of infusion within 15 min of IV bolus)<br><br>Duration of treatment: 48 hours |                           |                  |              |

<sup>a</sup> Subjects with known severe renal impairment at baseline were excluded from the study.

<sup>b</sup> In subjects  $\geq 75$  years of age, no iv bolus was to be administered.

STEMI = ST-segment elevation myocardial infarction; IV = intravenous; SC = subcutaneous; PCI = percutaneous intervention; CrCl = creatinine clearance; NA = not applicable

### Study Results

The primary efficacy end point was the composite of death from any cause or myocardial reinfarction in the first 30 days after randomization. The efficacy data provided below, show that the rate of the primary efficacy end point (death or myocardial re-infarction) was 9.9% in the enoxaparin group, as compared with 12.0% in the unfractionated heparin group, that is a 2.1% reduction in the absolute risk, representing a 17% reduction in the relative risk, ( $P < 0.001$ ).

**Table 36 - Efficacy of LOVENOX Injection in the treatment of acute ST-segment Elevation Myocardial Infarction**

| Primary Endpoints                                             | Enoxaparin (N=10,256) n (%) | HEPARIN (N=10,223) n (%) | Reduction in Absolute Risk (%) | Relative Risk (95% CI) | p-value |
|---------------------------------------------------------------|-----------------------------|--------------------------|--------------------------------|------------------------|---------|
| Outcome at 48 hours                                           |                             |                          |                                |                        |         |
| Death or Myocardial Re-infarction                             | 478 (4.7)                   | 531 (5.2)                | 0.5                            | 0.90 (0.80 to 1.01)    | 0.08    |
| Death                                                         | 383 (3.7)                   | 390 (3.8)                | 0.1                            | 0.98 (0.85 to 1.12)    | 0.76    |
| Myocardial Re-infarction                                      | 102 (1.0)                   | 156 (1.5)                | 0.5                            | 0.65 (0.51 to 0.84)    | <0.001  |
| Urgent Revascularization                                      | 74 (0.7)                    | 96 (0.9)                 | 0.2                            | 0.77 (0.57 to 1.04)    | 0.09    |
| Death or Myocardial Re-infarction or Urgent Revascularization | 548 (5.3)                   | 622 (6.1)                | 0.8                            | 0.88 (0.79 to 0.98)    | 0.02    |
| Outcome at 8 Days                                             |                             |                          |                                |                        |         |
| Death or Myocardial Re-infarction                             | 740 (7.2)                   | 954 (9.3)                | 2.1                            | 0.77 (0.71 to 0.85)    | <0.001  |
| Death                                                         | 559 (5.5)                   | 605 (5.9)                | 0.4                            | 0.92 (0.82 to 1.03)    | 0.15    |
| Myocardial Re-infarction                                      | 204 (2.0)                   | 379 (3.7)                | 1.7                            | 0.54 (0.45 to 0.63)    | <0.001  |
| Urgent Revascularization                                      | 145 (1.4)                   | 247 (2.4)                | 1.0                            | 0.59 (0.48 to 0.72)    | <0.001  |
| Death or Myocardial Re-infarction or Urgent Revascularization | 874 (8.5)                   | 1181 (11.6)              | 3.1                            | 0.74 (0.68 to 0.80)    | <0.001  |

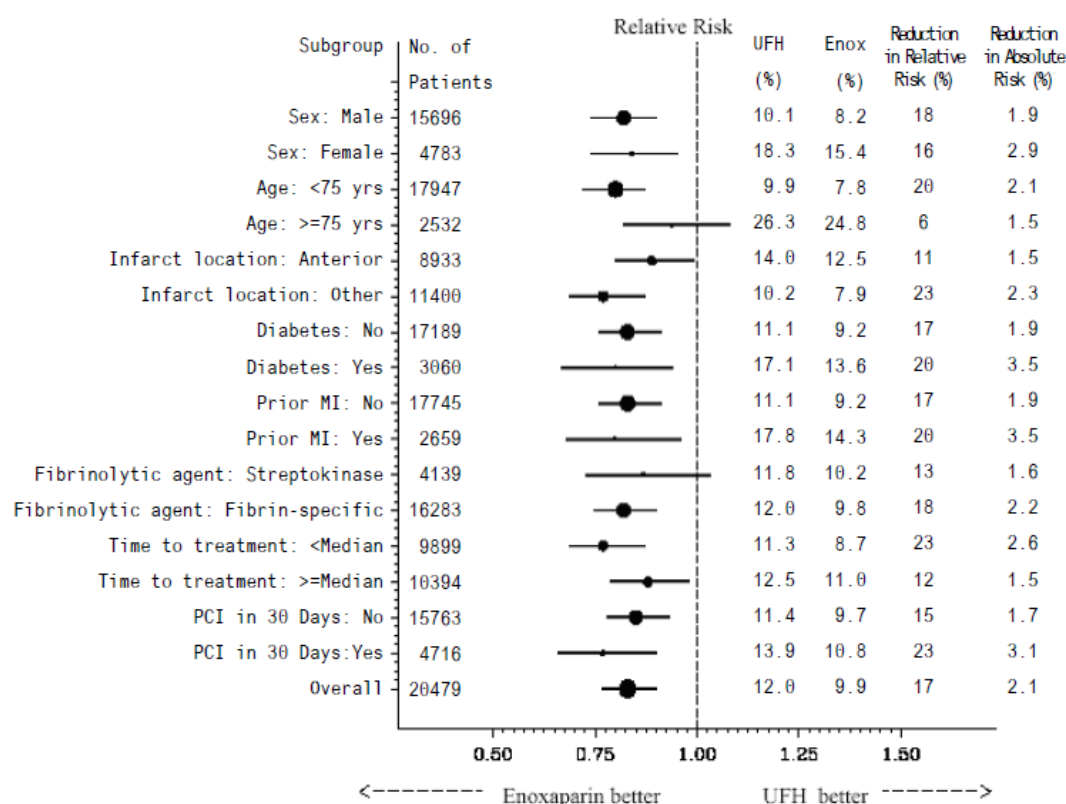
| Primary Endpoints                                                    | Enoxaparin<br>(N=10,256)<br>n (%) | HEPARIN<br>(N=10,223)<br>n (%) | Reduction<br>in Absolute<br>Risk (%) | Relative Risk (95%<br>CI)  | p-value          |
|----------------------------------------------------------------------|-----------------------------------|--------------------------------|--------------------------------------|----------------------------|------------------|
| Outcome at 30 Days                                                   |                                   |                                |                                      |                            |                  |
| <b>Primary efficacy endpoint (Death or Myocardial Re-infarction)</b> | <b>1017 (9.9)</b>                 | <b>1223 (12.0)</b>             | <b>2.1</b>                           | <b>0.83 (0.77 to 0.90)</b> | <b>&lt;0.001</b> |
| Death                                                                | 708 (6.9)                         | 765 (7.5)                      | 0.6                                  | 0.92 (0.84 to 1.02)        | 0.11             |
| Myocardial Re-infarction                                             | 352 (3.4)                         | 508 (5.0)                      | 1.6                                  | 0.69 (0.60 to 0.79)        | <0.001           |
| Urgent Revascularization                                             | 213 (2.1)                         | 286 (2.8)                      | 0.7                                  | 0.74 (0.62 to 0.88)        | <0.001           |
| Death or Myocardial Re-infarction or Urgent Revascularization        | 1199 (11.7)                       | 1479 (14.5)                    | 2.8                                  | 0.81 (0.75 to 0.87)        | <0.001           |

Note: Urgent revascularization denotes episodes of recurrent myocardial ischemia (without infarction) leading to the clinical decision to perform coronary revascularization during the same hospitalization. CI denotes confidence intervals.

The treatment benefits of enoxaparin, evident for a number of efficacy outcomes, emerged at 48 hours, at which time there was a 35% reduction in the relative risk of myocardial reinfarction, representing an absolute risk reduction of 0.5%, as compared with treatment with unfractionated heparin ( $p < 0.0001$ ).

The beneficial effect of enoxaparin on the primary end point was consistent across key subgroups including age, gender, infarct location, history of diabetes, history of prior myocardial infarction, fibrinolytic administered, and time to treatment with study drug (see figure below).

**Figure 1: Relative Risks of and Absolute Event Rates for the Primary End Point at 30 Days in Various Subgroups**



The primary efficacy end point was the composite of death from any cause or myocardial reinfarction in the first 30 days. The overall treatment effect of enoxaparin as compared to the unfractionated heparin is

shown at the bottom of the figure. For each subgroup, the circle is proportional to the number and represents the point estimate of the treatment effect and the horizontal lines represent the 95 percent confidence intervals. Fibrin-specific fibrinolytic agents included alteplase, tenecteplase and reteplase. Time to treatment indicates the time from the onset of symptoms to the administration of study drug (median, 3.2 hours). Although there was some variation in the estimate of the treatment effect of enoxaparin on the primary endpoint across the subgroups shown, all *p*-values in tests for interaction were non significant.

There was a significant treatment benefit of enoxaparin, as compared with unfractionated heparin, in patients who underwent percutaneous coronary intervention within 30 days after randomization (23% relative risk reduction, representing an absolute risk reduction of 3.1%) or who were treated medically (15 % relative risk reduction, representing an absolute risk reduction of 1.7%, *p* = 0.27 for interaction).

The rate of the 30-day composite endpoint of death, myocardial re-infarction or ICH (a measure of net clinical benefit) was significantly lower (*p*<0.0001) in the enoxaparin group (10.1%) as compared to the heparin group (12.2%), representing a 2.1% absolute risk reduction and a 17% relative risk reduction in favor of treatment with LOVENOX.

### **Benefit of LOVENOX beyond 30 days post-treatment period, up to 1 year for the treatment of acute STEMI**

The ExTRACT – 1 year follow-up study evaluated the benefits of LOVENOX beyond 30 days post-treatment period up to 1 year.

#### **Study demographics and trial design [ExTRACT – 1-year follow-up]**

In order to determine whether or not the clinical benefits of LOVENOX shown in the early phase of ExTRACT trial persisted over-time, a one-year follow-up survey was undertaken in all patients enrolled in the ExTRACT study. The main objective of the follow-up period was to assess the subject status at 6-months and 12-months (mortality, myocardial re-infarction, disabling stroke, or re- hospitalization). The one-year follow-up period was defined as time of randomization through one-year assessment or last contact (documented by phone contact or patient record). Complete 1 year information from 18 160 (88.7%) patients was available. Two thousand three hundred and twelve (11.3%) patients discontinued from the study. The primary reasons for discontinuation are: death 2115 (10.3%), discontinuation for other reasons 90 (0.4%), lost to follow-up 107 (0.5 %).

**Table 37 - Summary of patient demographics for ExTRACT – 1-year follow-up**

| Study #                    | Trial Design              | Dosage, route of administration and duration                                                                                                                  | Study subjects (n=number)                                                                             | Mean age (Range)                             | Gender (M/F)                           |
|----------------------------|---------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|----------------------------------------------|----------------------------------------|
| ExTRACT – 1-year follow-up | 1 year collection of data | See table 35 above for ExTRACT Dosage, route of administration and duration<br><br>During the additional follow-up period subjects were off study medication. | Total: 20 479<br><br>18 160 (with long term follow-up)<br><br>enoxaparin : 9098<br><br>heparin : 9062 | <br><br><br>58.8 (20-99)<br><br>58.9 (20-92) | <br><br><br>7102/1996<br><br>7160/1902 |

### Study results

There was a statistically significant difference ( $p = 0.0111$ , log-rank test, hazard ratio [HR] = 0.92) in favor of the enoxaparin group compared with the UFH group with respect to time to death or myocardial re-infarction at 12 months as assessed by survival analysis (log-rank test).

The beneficial effect of enoxaparin on the composite primary end point (death or myocardial reinfarction) observed during the first 30 days was maintained over a 12 month follow-up period (see Figure 2). The relative risk reduction in the composite endpoint of death from any cause or myocardial re-infarction observed in the first 30 days after randomization and at 12 months was 17% and 8% respectively.

**Table 38 - Results from Cox Regression and Kaplan Meir over 12 months – ITT population**

| Parameter                                              | Enoxaparin   |             | UFH          |             | Enox vs UFH<br>Hazard ratio <sup>b</sup> | 95% CI of HR       | p-value <sup>a</sup> |
|--------------------------------------------------------|--------------|-------------|--------------|-------------|------------------------------------------|--------------------|----------------------|
|                                                        | N            | N           | N            | n           |                                          |                    |                      |
| <b>Main Clinical endpoint</b>                          | <b>10256</b> |             | <b>10233</b> |             |                                          |                    |                      |
| <b>Death or myocardial re-infarction</b>               |              | <b>1614</b> |              | <b>1732</b> | <b>0.92</b>                              | <b>[0.86-0.98]</b> | <b>0.0111</b>        |
| Additional component endpoints                         | 10256        |             | 10233        |             |                                          |                    |                      |
| Death or myocardial re-infarction, or disabling stroke |              | 1638        |              | 1765        | 0.91                                     | [0.85-0.98]        | 0.0069               |
| Individual component endpoints                         | 10256        |             | 10233        |             |                                          |                    |                      |
| Death                                                  |              | 1075        |              | 1085        | 0.98                                     | [0.90 – 1.07]      | 0.7145               |
| Myocardial re-infarction                               |              | 666         |              | 775         | 0.84                                     | [0.76 – 0.94]      | 0.0013               |
| Disabling stroke                                       |              | 112         |              | 115         | 0.97                                     | [0.75 – 1.26]      | 0.8121               |
| Re-hospitalization                                     |              | 2873        |              | 2742        | 1.05                                     | [0.99 – 1.10]      | 0.0849               |

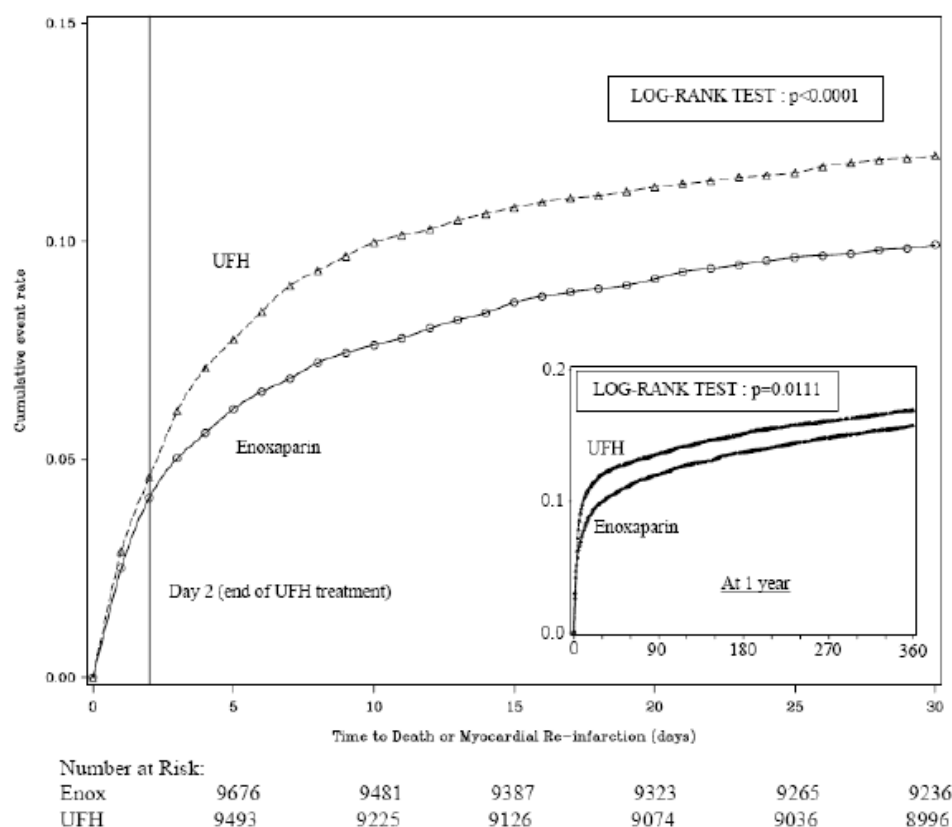
Note: Re-hospitalization was for a cardiac/vascular reason.

<sup>a</sup> log-rank test

<sup>b</sup> unadjusted Cox Regression

ITT = intent to treat population; UFH = unfractionated heparin; Enox = enoxaparin, vs = versus, N = population size; n = number of subjects with events

CI = confidence interval; HR = hazard ratio

**Figure 2: Kaplan-Meier plot - death or myocardial re-infarction at 30 days and at 1 year - ITT population**

### Prevention of thrombus formation in the extracorporeal circulation during hemodialysis

Information to support the safety and efficacy of LOVENOX in the prevention of thrombus formation in the extracorporeal circulation during hemodialysis comes from three published studies.

## 15 MICROBIOLOGY

No microbiological information is required for this drug product.

## 16 NON-CLINICAL TOXICOLOGY

REDESCA (enoxaparin sodium) is a biosimilar biologic drug, where the animal toxicology properties of enoxaparin sodium have already been described for the reference biologic drug. Therefore, this section summarizes the results of animal toxicology studies performed with reference biologic drug.

### Acute Toxicity

Acute toxicity studies with enoxaparin sodium were carried out with both sexes of several animal species. The results of these studies are presented in table below.

**Table 39 - The results of acute toxicity studies with enoxaparin sodium**

| Species                            | Route | LD50 (mg/kg)      |
|------------------------------------|-------|-------------------|
| <i>Mouse (NMRI strain)</i>         |       |                   |
| M (N=40)                           | s.c.  | 6700 (5027-8930)  |
| F (N=40)                           | s.c.  | 8100 (6326-10371) |
| M (N=35)                           | i.v.  | 2340 (2066-2650)  |
| F (N= 30)                          | i.v.  | 2340 (2122-2580)  |
| <i>Rat (Sprague-Dawley strain)</i> |       |                   |
| M (N=40)                           | s.c.  | >46.4*            |
| F (N= 40)                          | s.c.  | >46.4*            |
| M (N=35)                           | i.v.  | 1660 (1518-1816)  |
| F (N= 40)                          | i.v.  | 1810 (1625-2017)  |
| <i>Dog (Beagle)</i>                |       |                   |
| (N=3)                              | i.v.  | >2150             |

\*Mortality not linearly related.

Acute signs of toxicity in mice and rats following i.v. dosing of enoxaparin included ataxia, dyspnea with slight mydriasis, short tonic convulsions and death. Following s.c. dosing, acute signs of toxicity included ataxia, dyspnea, cyanosis and, occasionally, ventral decubitus, coma and death. In dogs, signs of toxicity included polypnea, tachycardia, mild agitation, sedation, lateral decubitus, ptialism, mydriasis and loss of oculopalpebral reflex; all dogs recovered completely.

#### Local Tolerance and Sensitization

Single high dose subcutaneous injections of 0.6 mL enoxaparin injection solution (equivalent to an anti-Xa activity of approximately 100 mg) were well tolerated by 6 Beagle dogs, with no signs of local irritation or allergic potential. Likewise, single intradermal injections of up to 50% enoxaparin for 1 to 3 weeks, followed by epicutaneous application of the drug, revealed no allergenic potential or local intolerance in 40 male Pirbright white guinea pigs.

#### Long Term Toxicity

Subacute and chronic toxicity studies were conducted in rats, dogs and monkeys. There were no species differences in the toxicity of enoxaparin; in all animals there were changes in hematology values and organ weights, reflecting the physiological adaptation of animals to long term anticoagulant treatment and resulting hemorrhage.

In subacute studies, the highest non-toxic s.c. doses over 13 weeks were 3 mg/kg/day in rats and 6.5 mg/kg/day in dogs. In 26-week studies, the highest non-toxic dose was 3 mg/kg/day in both rats and monkeys.

#### *In the Rat*

##### **13-Week, Subcutaneous Administration**

Wistar rats received enoxaparin in doses of 3, 6.5 or 15 mg/kg/day for 13 weeks (30 rats per dose). Hematology values remained within the normal limits during the first 6 weeks, but after 13 weeks of treatment, animals in the highest dose group showed moderate decreases in hemoglobin, red cell count, packed cell volume and small increases in WBC and platelets. With the highest dose, there were slight increases in LDH, alpha hydroxy butyric dehydrogenase (HBDH) and slight decreases in alkaline phosphatase, sodium ion and chloride ion.

Histopathological examination revealed dose-related hemorrhage and hematomas at the injection site.

**26-Week, Subcutaneous Administration**

Groups of Sprague-Dawley rats (30 animals per group) received 0, 3, 10 and 30 mg/kg/day s.c. for 26 weeks.

Mortality rates of about 30% occurred among animals taking the two highest doses (versus 2% of control animals and 3% of animals on the lowest dose).

Animals receiving the highest dose exhibited decreased concentrations of hemoglobin, hematocrit and RBC and a higher incidence of prothrombin consumption times of less than 100 seconds. Platelet counts were elevated in all treated animals, but normalized during a post-treatment recovery period. These hematology responses were considered normal sequelae of anticoagulant activity, rather than toxic manifestations. Cholesterol levels in all males and in high dose females were elevated above control values in both treatment and recovery phases.

Terminal absolute and relative organ weights for the spleen and liver were elevated in dose related manner. Histomorphological examinations revealed bleeding at the injection site, but no toxicopathological effects.

**26-Week, Intravenous Administration**

Sprague-Dawley rats (25-30 animals per dose) initially received 0, 1, 10, 30 and 90 mg/kg/day, but after 4 weeks, the two highest doses were reduced to 20 and 40 mg/kg/day because of excessive anticoagulation and toxicity.

In all animals, inflammation, hemorrhage and necrosis were observed at the injection site. Mortality was dose related, death being due to internal hemorrhaging, particularly into the abdominal cavity.

Chronic enoxaparin administration induced decreases in hemoglobin, hematocrit and RBC and increases in platelet and reticulocyte counts, the latter in the highest dose group only. All values normalized during the post-treatment recovery period. With the highest doses, serum urea was elevated, which was likely a result of tubular nephrosis of the kidney and renal capsular hemorrhage seen at autopsy. In addition, organ weights of the spleen, adrenal gland, kidney, heart and liver were increased. Autopsy revealed tubular nephrosis of the kidney and renal capsular hemorrhage.

*In the Dog***13-Week, Subcutaneous Administration**

Beagle dogs (6 animals per dose) received enoxaparin for 13 weeks in doses of 0, 3, 6.5 and 15 mg/kg/day s.c.

There were no deaths and no drug related effects on body weight, food consumption, ocular examination, plasma parathormone (PTH) levels or terminal organ weights.

Mild dose-related local hemorrhaging occurred at the injection site, but almost no subcutaneous hemorrhaging.

Hematology and biochemistry values remained normal throughout the study and histopathological findings at necropsy revealed only mild parathyroid hyperplasia in dogs given the highest dose.

*In the Monkey***26-Week, Subcutaneous Administration**

Cynomolgus monkeys (7 animals/sex/group) were given enoxaparin in doses of 0, 3, 10 and 20 mg/kg/day s.c. for 26 weeks. After 6 months, 2 animals/sex/group were selected for 6 weeks of observation of recovery.

Two high dose males died spontaneously after 10 and 172 days. Another high dose male and 3 high dose females were killed in extremis. All deaths were the result of hemorrhaging.

Dose-related inflammation of the injection site was observed, but symptoms generally disappeared by the end of the recovery period.

Among surviving animals, body weight and food consumption remained normal. Hematology values of RBC, hemoglobin and hematocrit, prothrombin time decreased, while thrombin time and eosinophilic sedimentation rates were elevated in mid- and high dose animals. Urinalysis and biochemistry values remained within normal limits.

Organ weights for the kidney, liver and spleen were elevated in the mid- and high dose animals and remained elevated in the male animals of the high dose group after the recovery period.

**26-Week, Intravenous Administration**

Cynomolgus monkeys (4-5 animals per dose) were given 0, 5, 10 or 20 mg/kg enoxaparin i.v. for 26 weeks. One animal in each group was retained for 4 weeks for observation of recovery.

One monkey in the high dose group died, although it had had no excessive bleeding or abnormal histopathological signs at autopsy.

No signs of toxicity were observed with the 5 mg/kg dose. Other doses produced dose-related inflammation and hemorrhaging at the injection site. Swelling of the arms or legs gradually disappeared by the end of the dosing period.

During treatment, hematology, biochemistry and urinalysis values in all treated animals corresponded to those of control animals. Histopathological examination revealed no drug related changes in individual organs.

**Mutagenicity**

Enoxaparin exhibited no mutagenic activity when tested *in vitro* by the Ames test in 5 strains of *S. typhimurium*. Likewise, no mutagenic activity could be demonstrated *in vitro* in a mammalian cell system, mouse lymphoma cells, with and without metabolic activation.

The clastogenic potential of enoxaparin was tested *in vitro* in human peripheral lymphocytes and *in vivo* in the bone marrow cells of rats. No clastogenic activity could be demonstrated by either method.

**Reproduction and Teratology***Fertility and Reproduction - In the Rat*

Reproductive performance was evaluated in 26 male and in 26 female sexually mature Sprague-Dawley rats (identified as the F<sub>0</sub> generation of animals). Starting 15 days before mating, all animals received 0, 3, 10 or 20 mg/kg/day enoxaparin subcutaneously. Treatment continued through mating, gestation and lactation to 4 days post-partum. One portion of the females was sacrificed 21 days after mating and another portion following the weaning of offspring.

Enoxaparin produced no adverse effects on the general condition of F<sub>0</sub> animals or on reproductive performance, gestation and parturition. Necropsy of dams revealed normal numbers of corpora lutea,

uterine contents and fetuses. The neonates (F<sub>1</sub> generation) exhibited no signs of toxicity and followed normal weight gain patterns. Fertility and reproductive performance of the untreated F<sub>1</sub> generation were normal and the fetal parameters of their offspring (F<sub>2</sub> generation) were normal.

In conclusion, enoxaparin, when given in doses of up to 20 mg/kg/day s.c. throughout a complete gametogenic cycle, pregnancy and lactation exerted no significant adverse effects on reproductive performance of treated F<sub>0</sub> animals or on the growth and reproduction of their untreated F<sub>1</sub> offspring.

#### *Teratology - In the Rat*

Female Sprague-Dawley rats (20 animals per dose) received enoxaparin by subcutaneous injection in doses of 3, 10 or 30 mg/kg/day from Days 6 to 15 of gestation. Control animals received the physiological saline vehicle. All dams were killed on Day 21 of gestation.

Maternal necropsy showed no evidence of adverse effects on corpora lutea or uterine contents. Fetuses from the 3 and 10 mg/kg dose groups showed no treatment-related abnormalities. In the high dose group, there was a slightly higher incidence of large fetuses as compared to historical control values and a slightly increased incidence of hydronephrosis and unilateral hydroureter.

Also in the high dose group, there was a slightly higher incidence of fetuses with dilated brain ventricles, thought to be associated with low fetal body weight.

In another study, female Sprague-Dawley rats (24 animals per dose) received enoxaparin by the intravenous route in doses of 0, 10, 40 and 160 mg/kg/day from Days 6 to 15 of gestation. Fetal necropsy was performed on the 20th day of gestation. Doses of 10 and 40 mg/kg/day exerted no adverse systemic effects on dams and did not adversely influence prenatal development.

The 160 mg/kg/day dose was within the low lethal range for the dams and 2 animals died from loss of blood. Fertility results from the surviving dams did not differ significantly from the controls or lower dose groups.

There were no indications of teratogenic effects in rats with enoxaparin by either the s.c. or i.v. routes, even with the highest doses.

#### *Teratology - In the Rabbit*

Female New Zealand rabbits (14 animals per dose) received enoxaparin by subcutaneous injection in doses of 0, 3, 10 and 30 mg/kg/day from Days 6 to 18 of gestation. Dams were sacrificed on Day 29 of gestation.

Two dams (given 10 mg/kg/day) aborted all fetuses during treatment. One female each in the 10 and 30 mg/kg/day groups totally resorbed their litters.

Necropsy examination of the other animals revealed no significant differences between enoxaparin- and vehicle-treated dams with respect to corpora lutea, uterine contents and number of fetuses. There was one abnormal fetus from the 3 mg/kg group, but this was considered unrelated to drug treatment.

In a second study, female New Zealand rabbits (12 animals per dose) received enoxaparin by the intravenous route in doses of 0, 10, 40 or 160 mg/kg/day from Days 6 to 18 of gestation. Dams were killed on Day 29 of gestation.

One rabbit in the highest dose group died from multiple systemic hemorrhages and another animal aborted.

On gestation Day 19, there were no adverse maternal or fetal effects for the groups given 10 and 40 mg/kg/day. In the group given 160 mg/kg/day, there were no significant differences in the number of

corpora lutea or uterine implantations compared to vehicle control values. Four dams from this group resorbed all fetuses. The group mean resorption rate in the high dose group was 56.8% (versus 9.8% for the control group).

There were no teratogenic effects in rabbits by either route of administration. In the high-dose intravenous group, the frequency of vertebral malformations was slightly increased, but still within the normal range for this species.

*Perinatal and Postnatal Development - In the Rat*

Enoxaparin was administered to Sprague-Dawley rats (20 animals per dose) in doses of 0, 3, 10 or 20 mg/kg/day s.c. from the 15th day of gestation to the 21st day of lactation. Offspring were observed from birth to weaning.

Litter size, viability and general condition of the offspring were unaffected by treatment.

Postnatal body weights and body weight gain to weaning were marginally reduced in the low and mid-dose groups, but were significantly reduced in the high-dose group. Terminal examination of offspring revealed no macroscopic changes in any of the groups.

## **17 SUPPORTING PRODUCT MONOGRAPHS**

1. Lovenox and Lovenox HP (solution for injection, 100 mg/ml, 150 mg/ml), Submission Control No.: 209807, Product Monograph, Sanofi-Aventis Canada Inc., December 19, 2019

**PATIENT MEDICATION INFORMATION (100 mg/mL pre-filled syringes)****READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE****Pr REDESCA®****Enoxaparin sodium solution for injection****Pre-filled syringes**

Read this carefully before you start taking REDESCA and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about REDESCA.

*REDESCA is a biosimilar biologic drug (biosimilar) to the reference biologic drug Lovenox®. A biosimilar is authorized based on its similarity to a reference biologic drug that was already authorized for sale.*

**What is REDESCA used for?**

- to prevent the formation of deep vein thrombosis (blood clots), which can occur as a complication of orthopedic surgery such as hip or knee surgery or of intra-abdominal (inside the body cavity below diaphragm which contains stomach, intestines, liver, and other organs) surgeries;
- to prevent the formation of deep vein thrombosis in medical patients who are at risk of thromboembolic (blockage of blood vessel by a blood clot) complications due to severely restricted mobility during acute illnesses (cardiac insufficiency [reduced ability of heart to pump blood], respiratory failure or severe chest infections);
- to treat deep vein thrombosis with or without pulmonary embolism (blockage of blood vessel in the lungs);
- to treat unstable angina and non-Q-wave myocardial infarction (death of a part of the heart muscle that does not involve full thickness of the heart wall), concurrently with acetylsalicylic acid (ASA);
- to treat acute ST-segment Elevation Myocardial Infarction (STEMI), a particular form of heart attack. This indication includes patients to be managed medically or those with subsequent Percutaneous Coronary Intervention (PCI), a procedure that opens up a coronary artery (blood vessel that brings blood and oxygen to the heart muscle) and restores blood flow;
- to prevent clotting in the extra-corporeal circulation during hemodialysis.

**How does REDESCA work?**

REDESCA is an antithrombotic drug. This means that REDESCA helps to prevent blood clots from forming in patients who have either undergone surgery or are suffering from a medical condition that limits their mobility. It can also treat existing blood clots in deep veins or in unstable coronary artery disease (Unstable Angina or non Q-wave Myocardial Infarction).

**What are the ingredients in REDESCA?**

Medicinal ingredient: enoxaparin sodium (a low molecular-weight heparin)

Non-medicinal ingredient: water for injection

**REDESCA comes in the following dosage forms:**

REDESCA 100 mg/mL is available in pre-filled syringes offered with a system that shields the needle after injection:

- Single dose 30 mg/0.3 mL pre-filled syringes with protective shield;
- Single dose 40 mg/0.4 mL pre-filled syringes with protective shield;
- Single dose 60 mg/0.6 mL pre-filled syringes with protective shield;
- Single dose 80 mg/0.8 mL pre-filled syringes with protective shield;

- Single dose 100 mg/mL pre-filled syringes with protective shield.

**Do not use REDESCA if:**

- you have a known allergy to REDESCA or any of its constituents;
- you have a known allergy to any other low molecular weight heparins and/or heparin;
- you have thrombocytopenia (a severe decrease in the number of platelets in the blood); history (within the past 100 days) of heparin-induced thrombocytopenia (HIT) (a blood clotting disorder caused by heparin);
- you have bacterial endocarditis (bacterial infection inside of the heart);
- you have active bleeding;
- you have a major clotting disorder;
- you have gastric or duodenal ulcer (defect of the internal walls of the stomach or small intestine);
- you have cerebrovascular accident (except if there are systemic emboli);
- you have severe uncontrolled hypertension (high blood pressure);
- you have eye problems due to diabetes (diabetic retinopathy) or hemorrhage (bleeding);
- you have a tendency to bleeding regardless of the reason;
- you have injury or surgery on the brain, spinal cord, eyes and ears;
- you have kidney problems;
- you have liver problems;
- you have spinal/epidural anesthesia contraindicated where repeated treatment doses of REDESCA (1 mg/kg every 12 hours or 1.5 mg/kg once daily) are required, due to an increased risk of bleeding;
- you have other conditions or diseases involving an increased risk of bleeding.

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take REDESCA. Talk about any health conditions or problems you may have, including if you:**

- have prosthetic (artificial) heart valve;
- have stroke (cerebrovascular accident);
- have a known allergy to REDESCA or any of its constituents, or to other low molecular weight heparins and/or heparin;
- have thrombocytopenia (a severe decrease in the number of platelets in the blood), a history of heparin-induced thrombocytopenia (HIT) (a blood clotting disorder caused by heparin);
- have bacterial endocarditis (bacterial infection inside of the heart);
- have a major clotting disorder;
- have gastric or duodenal ulcer (defect of the internal walls of the stomach or small intestine);
- have hypertension (high blood pressure);
- have a tendency to bleeding regardless of the reason;
- have an injury or surgery (spinal surgery with spinal/epidural anesthesia) involving the central nervous system, eyes or ears;
- have spinal defect (or deformity);
- have kidney problems;
- have liver problems;
- have eye problems due to diabetes or hemorrhage (bleeding).

You should also inform your doctor at once if you are pregnant or if you are breast-feeding, so he can evaluate the possible risks to you and the infant.

**Certain medications may intensify the anticoagulant effect (increase the anti-clotting effect) of REDESCA. Therefore, it is important for you to advise your doctor of all drugs that you are presently taking.**

**It is necessary that you follow the instructions of your doctor or nurse carefully. Only give yourself the injections prescribed and do so the entire time period specified by your doctor.**

**Do not take any drugs other than those prescribed by your doctor while you are taking REDESCA.**

**If you need to consult with another doctor or see your dentist, be absolutely sure to tell them that you are being treated with REDESCA.**

**Tell your healthcare professional about all medicines you are presently taking, including any vitamins, minerals, natural supplements or alternative medicines.**

**The following may interact with REDESCA:**

- Acetylsalicylic acid (ASA), salicylates, and nonsteroidal anti-inflammatories (e.g. diclofenac, ibuprofen, ketorolac);
- Prednisolone;
- Dextran, vitamin K antagonists, clopidogrel, ticlopidine and dipyridamole.

**How to take REDESCA:**

REDESCA is a prescription drug and must be used as directed. Usually it is administered as a subcutaneous injection, which means the injection is made just under the surface of the skin. For some conditions, REDESCA may be administered as an intravenous (IV) injection. REDESCA must NOT be administered by the intramuscular route.

**Detailed instructions on how to inject REDESCA are provided in “Instructions for Use”.**

**Usual dose:**

Hip or Knee Replacement Surgery: while you are in the hospital, your doctor or a nurse will give your first injection within 24 hours after your operation, so as to prevent blood clots from forming. After that, your doctor or a nurse will give you 2 subcutaneous injections every day (one injection every 12 hours) while you are in hospital.

In case of hip replacement surgery, after completing the treatment with 2 subcutaneous injections per day, your doctor may ask you to take 1 subcutaneous injection every day for the following days at home or in hospital for an additional 3 weeks.

Abdominal or Colorectal Surgery: while you are in the hospital, your doctor or a nurse will give your first injection 2 hours prior to surgery. After that, your doctor or a nurse will give you 1 subcutaneous injection once a day while you are in hospital, your doctor may ask you to continue to take 1 subcutaneous injection every day for up to 4 weeks.

Medical Patients: while you are in the hospital, your doctor or a nurse will give you 1 subcutaneous injection once a day. The usual duration of administration is 6 to 11 days.

Treatment of Deep Vein Thrombosis, with or without Embolism: while you are in the hospital, your doctor or a nurse will give you 1 subcutaneous injection once or twice daily for about 10 days.

Treatment of Unstable Angina or Non-Q-Wave Myocardial Infarction: while you are in the hospital, your doctor or a nurse will give you 2 subcutaneous injections every day (one injection every 12 hours) along with oral ASA (100 to 325 mg once daily) for a minimum of 2 days.

Treatment of acute ST-segment Elevation Myocardial Infarction (STEMI): while you are in the hospital, your doctor or a nurse will give you a single intravenous (IV) injection followed by 2 subcutaneous injections every day (one injection every 12 hours) along with oral ASA (75 to 325 mg once daily) for a minimum of 8 days, unless contraindicated.

It is possible that after you go home, you may need to continue your injections of REDESCA for a few days.

Prevention of thrombus formation in the extracorporeal circulation during hemodialysis: while you are in the hospital, your doctor or a nurse will inject REDESCA into the arterial line of the circuit at the beginning of the dialysis session. The effect of this dose is usually sufficient for a 4-hour session.

#### Overdose:

Accidental overdosage may result in hemorrhaging, which cannot be treated at home. Therefore, if you suspect that you have used too much REDESCA, call your doctor immediately even if you do not yet observe any unusual symptoms. Your doctor can then make arrangements to bring you to hospital for observation and/or treatment.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

#### Missed dose:

If you miss a dose of this medication by a few hours, take it as soon as you remember. However if you are close to the time of the next dose, skip the missed dose and proceed with the regular dosing schedule. Do not double doses. If you are unsure about how to proceed contact your doctor or your pharmacist.

#### What are possible side effects from using REDESCA?

These are not all the possible side effects you may feel when taking REDESCA. If you experience any side effects not listed here, tell your healthcare professional.

Administration of REDESCA may result in bleeding which can have serious or life-threatening consequences. Hemorrhagic strokes (bleeding inside of the brain) and serious intra-abdominal bleeding (bleeding into the body cavity below diaphragm which contains stomach, intestines, liver, and other organs) have been reported. REDESCA is generally well tolerated when used according to directions of use, nevertheless *e.g.* hair loss could occur. Long term use of REDESCA (greater than 3 months) may increase the risk of bone thinning (osteoporosis).

| Serious side effects and what to do about them                                                      |                                      |              |                                                 |
|-----------------------------------------------------------------------------------------------------|--------------------------------------|--------------|-------------------------------------------------|
| Symptom / effect                                                                                    | Talk to your healthcare professional |              | Stop taking drug and get immediate medical help |
|                                                                                                     | Only if severe                       | In all cases |                                                 |
| <b>VERY COMMON</b>                                                                                  |                                      |              |                                                 |
| Bleeding ( <i>e.g.</i> at site injection, nosebleeds, blood in urine, bloody stools, bleeding gums) |                                      |              | ✓                                               |
| Changes in the results of blood tests done to check your liver                                      |                                      | ✓            |                                                 |
| <b>COMMON</b>                                                                                       |                                      |              |                                                 |
| Headache                                                                                            | ✓                                    |              |                                                 |
| Purplish or reddish discolouration or pain around the injection site                                | ✓                                    |              |                                                 |

| Serious side effects and what to do about them                                                                                                                                      |                                      |              |                                                 |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|--------------|-------------------------------------------------|
| Symptom / effect                                                                                                                                                                    | Talk to your healthcare professional |              | Stop taking drug and get immediate medical help |
|                                                                                                                                                                                     | Only if severe                       | In all cases |                                                 |
| Spontaneous bruising (a bruise not caused by a blow or any apparent reason)                                                                                                         |                                      | ✓            |                                                 |
| <b>UNCOMMON</b><br>Abdominal pain                                                                                                                                                   |                                      | ✓            |                                                 |
| Signs of liver problems such as loss of appetite, dark urine, light-colored stools, yellowing of the skin or eyes (jaundice)                                                        |                                      | ✓            |                                                 |
| <b>RARE</b><br>Allergic reaction skin rash, angioedema (swelling of lips, face, throat and tongue, breathing difficulties) and anaphylactic/anaphylactoid reactions including shock |                                      |              | ✓                                               |
| Problems in controlling your bowels and/or bladder                                                                                                                                  |                                      | ✓            |                                                 |
| Tingling, numbness and muscular weakness (particularly in the lower part of your body) when you have had a spinal puncture or a spinal anaesthetic                                  |                                      |              | ✓                                               |
| <b>UNKNOWN</b><br>Chest pain or shortness of breath                                                                                                                                 |                                      |              | ✓                                               |
| Confusion                                                                                                                                                                           |                                      | ✓            |                                                 |
| Dizziness                                                                                                                                                                           |                                      | ✓            |                                                 |
| Pain or swelling in any part of your leg, foot or hip                                                                                                                               |                                      | ✓            |                                                 |
| Rapid or unusual heart beat                                                                                                                                                         |                                      |              | ✓                                               |
| Skin discolouration as caused by ruptured blood vessels                                                                                                                             |                                      | ✓            |                                                 |
| Vomiting                                                                                                                                                                            |                                      | ✓            |                                                 |

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

#### **Reporting Side Effects**

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

*NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

#### **Storage:**

Store below 25 C. Do NOT freeze.

Keep out of the reach and sight of children.

#### **If you want more information about REDESCA:**

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer's website ([www.valeopharma.com](http://www.valeopharma.com)), or by calling 1-855-694-0151.

#### **Instructions for use:**

**Instructions for self-injection of REDESCA.** Your doctor may want you to continue your REDESCA injections at home for a few days. **If so, he or a nurse will show you how to administer your REDESCA injections before you are released from hospital. It is essential that you follow these instructions exactly. If you have questions, be sure you ask your doctor or nurse to provide the explanations you require.**

Proper subcutaneous (under the skin) injection of REDESCA is essential to prevent pain and bruising at the injection site.

When at home, there is nothing for you to prepare. The syringe is pre-filled with the exact amount of drug required. Do not press on the plunger prior to injection.

REDESCA solution should be inspected visually for clarity, particulate matter, precipitation, discolouration, and leakage prior to administration. Do not use if solution shows haziness, particulate matter, discolouration or leakage.

The recommended site for injection is into the fat of the lower abdomen. This should be at least 5 centimeters away from your belly button and out towards your sides.

Prior to injection, wash your hands and cleanse (do not rub) the selected site for injection with an alcohol swab. Select a different site of the lower abdomen for each injection.

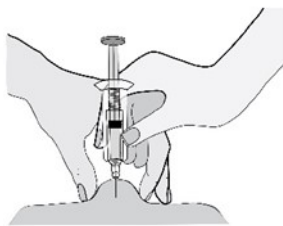
Carefully pull off the needle cap from the syringe. Throw away the cap. The syringe is pre-filled and ready to use.



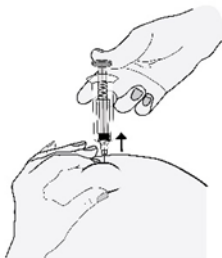
NOTE: To avoid the loss of drug when using the 30 and 40 mg pre-filled syringes, do not expel the air bubble from the syringe before the injection.

Once you have removed the cap, do not allow the needle to touch anything. This is to make sure the needle stays clean (sterile).

- Sit or lie down in a comfortable position and gather a fold of skin with your thumb and forefinger.
- Hold the syringe in the hand you write with (like a pencil) and with your other hand, gently pinch the cleaned area of your abdomen between your forefinger and thumb to make a fold in the skin.
- Make sure you hold the skin fold throughout the injection.
- Hold the syringe so that the needle is pointing downwards (vertically at a 90° angle). Insert the full length of the needle into the skin fold.

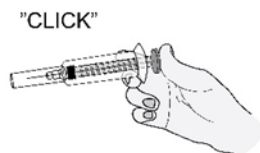


- Press down on the plunger with your finger. This will send the medicine into the fatty tissue of the stomach. Make sure you hold the skin fold throughout the injection.
- Remove the needle by pulling it straight out. Do not release the pressure on the plunger.



**To avoid bruising, do not rub the injection site after you have injected yourself.**

- Push hard on the plunger. The protective sleeve, which is in the form of a plastic cylinder, will be activated automatically and it will completely cover the needle.



- You should then safely dispose of the syringe and needle with its protective sleeve, so they remain out of reach of children.

This leaflet was prepared by Shenzhen Techdow Pharmaceutical Co., Ltd.

Last Revised:

**PATIENT MEDICATION INFORMATION (100 mg/mL in multiple dose vials)****READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE****Pr REDESCA®****Enoxaparin sodium solution for injection****Multiple dose vials**

Read this carefully before you start taking REDESCA and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about REDESCA.

*REDESCA is a biosimilar biologic drug (biosimilar) to the reference biologic drug Lovenox®. A biosimilar is authorized based on its similarity to a reference biologic drug that was already authorized for sale.*

**What is REDESCA used for?**

- to prevent the formation of deep vein thrombosis (blood clots), which can occur as a complication of orthopedic surgery such as hip or knee surgery or of intra-abdominal (inside the body cavity below diaphragm which contains stomach, intestines, liver, and other organs) surgeries;
- to prevent the formation of deep vein thrombosis in medical patients who are at risk of thromboembolic (blockage of blood vessel by a blood clot) complications due to severely restricted mobility during acute illnesses (cardiac insufficiency [reduced ability of heart to pump blood], respiratory failure or severe chest infections);
- to treat deep vein thrombosis with or without pulmonary embolism (blockage of blood vessel in the lungs);
- to treat unstable angina and non-Q-wave myocardial infarction (death of a part of the heart muscle that does not involve full thickness of the heart wall), concurrently with acetylsalicylic acid (ASA);
- to treat acute ST-segment Elevation Myocardial Infarction (STEMI), a particular form of heart attack. This indication includes patients to be managed medically or those with subsequent Percutaneous Coronary Intervention (PCI), a procedure that opens up a coronary artery (blood vessel that brings blood and oxygen to the heart muscle) and restores blood flow;
- to prevent clotting in the extra-corporeal circulation during hemodialysis.

**How does REDESCA work?**

REDESCA is an antithrombotic drug. This means that REDESCA helps to prevent blood clots from forming in patients who have either undergone surgery or are suffering from a medical condition that limits their mobility. It can also treat existing blood clots in deep veins or in unstable coronary artery disease (Unstable Angina or non Q-wave Myocardial Infarction).

**What are the ingredients in REDESCA?**

Medicinal ingredient: enoxaparin sodium (a low molecular-weight heparin)

Non-medicinal ingredients: water for injection, benzyl alcohol

**REDESCA comes in the following dosage form:**

REDESCA 100 mg/mL is available in multiple dose vials containing 300 mg/3 mL.

**Do not use REDESCA if:**

- you have a known allergy to REDESCA or any of its constituents, including benzyl alcohol;
- you have a known allergy to any other low molecular weight heparins and/or heparin;

- you have thrombocytopenia (a severe decrease in the number of platelets in the blood); history (within the past 100 days) of heparin-induced thrombocytopenia (HIT) (a blood clotting disorder caused by heparin);
- you have bacterial endocarditis (bacterial infection inside of the heart);
- you have active bleeding;
- you have a major clotting disorder;
- you have gastric or duodenal ulcer (defect of the internal walls of the stomach or small intestine);
- you have cerebrovascular accident (except if there are systemic emboli);
- you have severe uncontrolled hypertension (high blood pressure);
- you have eye problems due to diabetes (diabetic retinopathy) or hemorrhage (bleeding);
- you have a tendency to bleeding regardless of the reason;
- you have injury or surgery on the brain, spinal cord, eyes and ears;
- you have kidney problems;
- you have liver problems;
- you have spinal/epidural anesthesia contraindicated where repeated treatment doses of REDESCA (1 mg/kg every 12 hours or 1.5 mg/kg once daily) are required, due to an increased risk of bleeding;
- you have other conditions or diseases involving an increased risk of bleeding.

Because of the content of benzyl alcohol, REDESCA, when using multiple dose vials, must not be given to newborns or premature neonates.

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take REDESCA. Talk about any health conditions or problems you may have, including if you:**

- have prosthetic (artificial) heart valve;
- have stroke (cerebrovascular accident);
- have a known allergy to REDESCA or any of its constituents, or to other low molecular weight heparins and/or heparin;
- have thrombocytopenia (a severe decrease in the number of platelets in the blood), a history of heparin-induced thrombocytopenia (HIT) (a blood clotting disorder caused by heparin);
- have bacterial endocarditis (bacterial infection inside of the heart);
- have a major clotting disorder;
- have gastric or duodenal ulcer (defect of the internal walls of the stomach or small intestine);
- have hypertension (high blood pressure);
- have a tendency to bleeding regardless of the reason;
- have an injury or surgery (spinal surgery with spinal/epidural anesthesia) involving the central nervous system, eyes or ears;
- have spinal defect (or deformity);
- have kidney problems;
- have liver problems;
- have eye problems due to diabetes or hemorrhage (bleeding).

You should also inform your doctor at once if you are pregnant or if you are breast-feeding, so he can evaluate the possible risks to you and the infant.

Since REDESCA multiple dose vial is preserved with benzyl alcohol it should not be used in pregnant women.

Certain medications may intensify the anticoagulant effect (increase the anti-clotting effect) of REDESCA. Therefore, it is important for you to advise your doctor of all drugs that you are presently taking.

It is necessary that you follow the instructions of your doctor or nurse carefully. Only give yourself the injections prescribed and do so the entire time period specified by your doctor.

Do not take any drugs other than those prescribed by your doctor while you are taking REDESCA.

If you need to consult with another doctor or see your dentist, be absolutely sure to tell them that you are being treated with REDESCA.

Tell your healthcare professional about all medicines you are presently taking, including any vitamins, minerals, natural supplements or alternative medicines.

**The following may interact with REDESCA:**

- Acetylsalicylic acid (ASA), salicylates, and nonsteroidal anti-inflammatories (e.g. diclofenac, ibuprofen, ketorolac);
- Prednisolone;
- Dextran, vitamin K antagonists, clopidogrel, ticlopidine and dipyridamole.

**How to take REDESCA:**

REDESCA is a prescription drug and must be used as directed. Usually it is administered as a subcutaneous injection, which means the injection is made just under the surface of the skin. For some conditions, REDESCA may be administered as an intravenous (IV) injection. REDESCA must NOT be administered by the intramuscular route.

**Detailed instructions on how to inject REDESCA are provided in “Instructions for Use”.**

**Usual dose:**

Hip or Knee Replacement Surgery: while you are in the hospital, your doctor or a nurse will give your first injection within 24 hours after your operation, so as to prevent blood clots from forming. After that, your doctor or a nurse will give you 2 subcutaneous injections every day (one injection every 12 hours) while you are in hospital.

In case of hip replacement surgery, after completing the treatment with 2 subcutaneous injections per day, your doctor may ask you to take 1 subcutaneous injection every day for the following days at home or in hospital for an additional 3 weeks.

Abdominal or Colorectal Surgery: while you are in the hospital, your doctor or a nurse will give your first injection 2 hours prior to surgery. After that, your doctor or a nurse will give you 1 subcutaneous injection once a day while you are in hospital, your doctor may ask you to continue to take 1 subcutaneous injection every day for up to 4 weeks.

Medical Patients: while you are in the hospital, your doctor or a nurse will give you 1 subcutaneous injection once a day. The usual duration of administration is 6 to 11 days.

Treatment of Deep Vein Thrombosis, with or without Embolism: while you are in the hospital, your doctor or a nurse will give you 1 subcutaneous injection once or twice daily for about 10 days.

Treatment of Unstable Angina or Non-Q-Wave Myocardial Infarction: while you are in the hospital, your doctor or a nurse will give you 2 subcutaneous injections every day (one injection every 12 hours) along with oral ASA (100 to 325 mg once daily) for a minimum of 2 days.

Treatment of acute ST-segment Elevation Myocardial Infarction (STEMI): while you are in the hospital, your doctor or a nurse will give you a single intravenous (IV) injection followed by 2 subcutaneous

injections every day (one injection every 12 hours) along with oral ASA (75 to 325 mg once daily) for a minimum of 8 days, unless contraindicated.

It is possible that after you go home, you may need to continue your injections of REDESCA for a few days.

**Prevention of thrombus formation in the extracorporeal circulation during hemodialysis:** while you are in the hospital, your doctor or a nurse will inject REDESCA into the arterial line of the circuit at the beginning of the dialysis session. The effect of this dose is usually sufficient for a 4-hour session.

#### **Overdose:**

Accidental overdosage may result in hemorrhaging, which cannot be treated at home. Therefore, if you suspect that you have used too much REDESCA, call your doctor immediately even if you do not yet observe any unusual symptoms. Your doctor can then make arrangements to bring you to hospital for observation and/or treatment.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

#### **Missed dose:**

If you miss a dose of this medication by a few hours, take it as soon as you remember. However if you are close to the time of the next dose, skip the missed dose and proceed with the regular dosing schedule. Do not double doses. If you are unsure about how to proceed contact your doctor or your pharmacist.

#### **What are possible side effects from using REDESCA?**

These are not all the possible side effects you may feel when taking REDESCA. If you experience any side effects not listed here, tell your healthcare professional.

Administration of REDESCA may result in bleeding which can have serious or life-threatening consequences. Hemorrhagic strokes (bleeding inside of the brain) and serious intra-abdominal bleeding (bleeding into the body cavity below diaphragm which contains stomach, intestines, liver, and other organs) have been reported. REDESCA is generally well tolerated when used according to directions of use, nevertheless *e.g.* hair loss could occur. Long term use of REDESCA (greater than 3 months) may increase the risk of bone thinning (osteoporosis).

| Serious side effects and what to do about them                                                      |                                      |              |                                                 |
|-----------------------------------------------------------------------------------------------------|--------------------------------------|--------------|-------------------------------------------------|
| Symptom / effect                                                                                    | Talk to your healthcare professional |              | Stop taking drug and get immediate medical help |
|                                                                                                     | Only if severe                       | In all cases |                                                 |
| <b>VERY COMMON</b>                                                                                  |                                      |              |                                                 |
| Bleeding ( <i>e.g.</i> at site injection, nosebleeds, blood in urine, bloody stools, bleeding gums) |                                      |              | ✓                                               |
| Changes in the results of blood tests done to check your liver                                      |                                      | ✓            |                                                 |
| <b>COMMON</b>                                                                                       |                                      |              |                                                 |
| Headache                                                                                            | ✓                                    |              |                                                 |

| Serious side effects and what to do about them                                                                                                                                      |                                      |              |                                                 |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|--------------|-------------------------------------------------|
| Symptom / effect                                                                                                                                                                    | Talk to your healthcare professional |              | Stop taking drug and get immediate medical help |
|                                                                                                                                                                                     | Only if severe                       | In all cases |                                                 |
| Purplish or reddish discolouration or pain around the injection site                                                                                                                | ✓                                    |              |                                                 |
| Spontaneous bruising (a bruise not caused by a blow or any apparent reason)                                                                                                         |                                      | ✓            |                                                 |
| <b>UNCOMMON</b><br>Abdominal pain                                                                                                                                                   |                                      | ✓            |                                                 |
| Signs of liver problems such as loss of appetite, dark urine, light-colored stools, yellowing of the skin or eyes (jaundice)                                                        |                                      | ✓            |                                                 |
| <b>RARE</b><br>Allergic reaction skin rash, angioedema (swelling of lips, face, throat and tongue, breathing difficulties) and anaphylactic/anaphylactoid reactions including shock |                                      |              | ✓                                               |
| Problems in controlling your bowels and/or bladder                                                                                                                                  |                                      | ✓            |                                                 |
| Tingling, numbness and muscular weakness (particularly in the lower part of your body) when you have had a spinal puncture or a spinal anaesthetic                                  |                                      |              | ✓                                               |
| <b>UNKNOWN</b><br>Chest pain or shortness of breath                                                                                                                                 |                                      |              | ✓                                               |
| Confusion                                                                                                                                                                           |                                      | ✓            |                                                 |
| Dizziness                                                                                                                                                                           |                                      | ✓            |                                                 |
| Pain or swelling in any part of your leg, foot or hip                                                                                                                               |                                      | ✓            |                                                 |
| Rapid or unusual heart beat                                                                                                                                                         |                                      |              | ✓                                               |
| Skin discolouration as caused by ruptured blood vessels                                                                                                                             |                                      | ✓            |                                                 |

| Serious side effects and what to do about them |                                      |              |                                                 |
|------------------------------------------------|--------------------------------------|--------------|-------------------------------------------------|
| Symptom / effect                               | Talk to your healthcare professional |              | Stop taking drug and get immediate medical help |
|                                                | Only if severe                       | In all cases |                                                 |
| Vomiting                                       |                                      | ✓            |                                                 |

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

#### Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

*NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

#### Storage:

Store below 25 C. Do NOT freeze.

Do not store the multiple dose vials for more than 28 days after the first use.

Keep out of the reach and sight of children.

#### If you want more information about REDESCA:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer's website ([www.valeopharma.com](http://www.valeopharma.com)), or by calling 1-855-694-0151.

#### Instructions for use:

Your doctor may want you to continue your REDESCA injections at home for a few days. **If so, he or a nurse will show you how to administer your REDESCA injections before you are released from hospital. It is essential that you follow these instructions exactly. If you have questions, be sure you ask your doctor or nurse to provide the explanations you require.**

Proper subcutaneous (under the skin) injection of REDESCA is essential to prevent pain and bruising at the injection site.

#### Syringe use

Carefully follow the directions supplied by your health professional on the correct use of your syringes to:

- help avoid contamination and possible infection,
- obtain an accurate dose.

Do not share your syringes and needles with anyone including other family members. You may give another person a serious infection, or get a serious infection from them. Used syringes and needles should be disposed properly.

### **Preparing the dose**

1. To avoid medication errors, check the vial label before each injection.
2. REDESCA solution should be inspected visually for clarity, particulate matter, precipitation, discolouration, and leakage prior to administration. Do not use if solution shows haziness, particulate matter, discolouration or leakage.
3. Wash your hands.
4. If using a new vial, remove the protective cap, but DO NOT remove the stopper.
5. Wipe the top of the vial with an alcohol swab. Do not touch the vial stopper after wiping with the alcohol swab.
6. A new sterile syringe must be used for each injection.
7. Draw air into the syringe equal to your REDESCA dose. Put the needle through the rubber top of the REDESCA vial and inject the air into the vial.
8. Turn the vial and syringe upside down. Hold the vial and syringe firmly in one hand.
9. Make sure the tip of the needle is in the solution and withdraw the correct dose of REDESCA into the syringe.
10. Before removing the needle from the vial, check your syringe for air bubbles. If bubbles are present, hold the syringe straight up and tap its side until the bubbles float to the top. Push them out with the plunger and withdraw the correct dose.
11. Remove the needle from the vial. Do not let the needle touch anything prior to injection.
12. An empty vial must never be reused and must be properly discarded.

### **Injection**

The recommended site for injection is into the fat of the lower abdomen. This should be at least 5 centimeters away from your belly button and out towards your sides.

Prior to injection, cleanse (do not rub) the selected site for injection with an alcohol swab. Select a different site of the lower abdomen for each injection.

- Sit or lie down in a comfortable position and gather a fold of skin with your thumb and forefinger.
- Then holding the syringe at a right angle to the skin folded between your thumb and forefinger, insert the needle as far as it will go. Hold the skin fold throughout the injection process. Once the needle has been inserted, the syringe should not be moved.
- Push the plunger to inject REDESCA.
- Be sure the syringe is empty and the plunger is pushed all the way down before removing the syringe.
- Remove the needle at a right angle, by pulling it straight out.
- You can now let go of the skin fold and apply light pressure to the skin at the injection site for several seconds with an alcohol swab. This action will help lessen any oozing of REDESCA or bleeding. Do not rub the injection site.
- You should then safely dispose of the syringe and needle, so they remain out of reach of children.

This leaflet was prepared by Shenzhen Techdow Pharmaceutical Co., Ltd.

Last Revised:

**PATIENT MEDICATION INFORMATION** (150 mg/mL pre-filled syringes)**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE****Pr REDESCA HP®****Enoxaparin sodium solution for injection****Pre-filled syringes**

Read this carefully before you start taking REDESCA HP and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about REDESCA HP.

*REDESCA HP is a biosimilar biologic drug (biosimilar) to the reference biologic drug Lovenox®. A biosimilar is authorized based on its similarity to a reference biologic drug that was already authorized for sale.*

**What is REDESCA HP used for?**

- to prevent the formation of deep vein thrombosis (blood clots), which can occur as a complication of orthopedic surgery such as hip or knee surgery or of intra-abdominal (inside the body cavity below diaphragm which contains stomach, intestines, liver, and other organs) surgeries;
- to prevent the formation of deep vein thrombosis in medical patients who are at risk of thromboembolic (blockage of blood vessel by a blood clot) complications due to severely restricted mobility during acute illnesses (cardiac insufficiency [reduced ability of heart to pump blood], respiratory failure or severe chest infections);
- to treat deep vein thrombosis with or without pulmonary embolism (blockage of blood vessel in the lungs);
- to treat unstable angina and non-Q-wave myocardial infarction (death of a part of the heart muscle that does not involve full thickness of the heart wall), concurrently with acetylsalicylic acid (ASA);
- to treat acute ST-segment Elevation Myocardial Infarction (STEMI), a particular form of heart attack. This indication includes patients to be managed medically or those with subsequent Percutaneous Coronary Intervention (PCI), a procedure that opens up a coronary artery (blood vessel that brings blood and oxygen to the heart muscle) and restores blood flow;
- to prevent clotting in the extra-corporeal circulation during hemodialysis.

**How does REDESCA HP work?**

REDESCA HP is an antithrombotic drug. This means that REDESCA HP helps to prevent blood clots from forming in patients who have either undergone surgery or are suffering from a medical condition that limits their mobility. It can also treat existing blood clots in deep veins or in unstable coronary artery disease (Unstable Angina or non Q-wave Myocardial Infarction).

**What are the ingredients in REDESCA HP?**

Medicinal ingredient: enoxaparin sodium (a low molecular-weight heparin)

Non-medicinal ingredient: water for injection

**REDESCA HP comes in the following dosage forms:**

REDESCA HP 150 mg/mL is available in pre-filled syringes offered with a system that shields the needle after injection:

- Single dose 120 mg/0.8 mL pre-filled syringes with protective shield;
- Single dose 150 mg/mL pre-filled syringes with protective shield.

**Do not use REDESCA HP if:**

- you have a known allergy to REDESCA HP or any of its constituents;
- you have a known allergy to any other low molecular weight heparins and/or heparin;
- you have thrombocytopenia (a severe decrease in the number of platelets in the blood); history (within the past 100 days) of heparin-induced thrombocytopenia (HIT) (a blood clotting disorder caused by heparin);
- you have bacterial endocarditis (bacterial infection inside of the heart);
- you have active bleeding;
- you have a major clotting disorder;
- you have gastric or duodenal ulcer (defect of the internal walls of the stomach or small intestine);
- you have cerebrovascular accident (except if there are systemic emboli);
- you have severe uncontrolled hypertension (high blood pressure);
- you have eye problems due to diabetes (diabetic retinopathy) or hemorrhage (bleeding);
- you have a tendency to bleeding regardless of the reason;
- you have injury or surgery on the brain, spinal cord, eyes and ears;
- you have kidney problems;
- you have liver problems;
- you have spinal/epidural anesthesia contraindicated where repeated treatment doses of REDESCA HP (1 mg/kg every 12 hours or 1.5 mg/kg once daily) are required, due to an increased risk of bleeding;
- you have other conditions or diseases involving an increased risk of bleeding.

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take REDESCA HP. Talk about any health conditions or problems you may have, including if you:**

- have prosthetic (artificial) heart valve;
- have stroke (cerebrovascular accident);
- have a known allergy to REDESCA HP or any of its constituents, or to other low molecular weight heparins and/or heparin;
- have thrombocytopenia (a severe decrease in the number of platelets in the blood), a history of heparin-induced thrombocytopenia (HIT) (a blood clotting disorder caused by heparin);
- have bacterial endocarditis (bacterial infection inside of the heart);
- have a major clotting disorder;
- have gastric or duodenal ulcer (defect of the internal walls of the stomach or small intestine);
- have hypertension (high blood pressure);
- have a tendency to bleeding regardless of the reason;
- have an injury or surgery (spinal surgery with spinal/epidural anesthesia) involving the central nervous system, eyes or ears;
- have spinal defect (or deformity);
- have kidney problems;
- have liver problems;
- have eye problems due to diabetes or hemorrhage (bleeding).

You should also inform your doctor at once if you are pregnant or if you are breast-feeding, so he can evaluate the possible risks to you and the infant.

**Certain medications may intensify the anticoagulant effect (increase the anti-clotting effect) of REDESCA HP. Therefore, it is important for you to advise your doctor of all drugs that you are presently taking.**

**It is necessary that you follow the instructions of your doctor or nurse carefully. Only give yourself the injections prescribed and do so the entire time period specified by your doctor.**

**Do not take any drugs other than those prescribed by your doctor while you are taking REDESCA HP.**

**If you need to consult with another doctor or see your dentist, be absolutely sure to tell them that you are being treated with REDESCA HP.**

**Tell your healthcare professional about all medicines you are presently taking, including any vitamins, minerals, natural supplements or alternative medicines.**

**The following may interact with REDESCA HP:**

- Acetylsalicylic acid (ASA), salicylates, and nonsteroidal anti-inflammatories (e.g. diclofenac, ibuprofen, ketorolac);
- Prednisolone;
- Dextran, vitamin K antagonists, clopidogrel, ticlopidine and dipyridamole.

**How to take REDESCA HP:**

REDESCA HP is a prescription drug and must be used as directed. Usually it is administered as a subcutaneous injection, which means the injection is made just under the surface of the skin. For some conditions, REDESCA HP may be administered as an intravenous (IV) injection.

REDESCA HP must NOT be administered by the intramuscular route.

**Detailed instructions on how to inject REDESCA HP are provided in “Instructions for Use”.**

**Usual dose:**

Hip or Knee Replacement Surgery: while you are in the hospital, your doctor or a nurse will give your first injection within 24 hours after your operation, so as to prevent blood clots from forming. After that, your doctor or a nurse will give you 2 subcutaneous injections every day (one injection every 12 hours) while you are in hospital.

In case of hip replacement surgery, after completing the treatment with 2 subcutaneous injections per day, your doctor may ask you to take 1 subcutaneous injection every day for the following days at home or in hospital for an additional 3 weeks.

Abdominal or Colorectal Surgery: while you are in the hospital, your doctor or a nurse will give your first injection 2 hours prior to surgery. After that, your doctor or a nurse will give you 1 subcutaneous injection once a day while you are in hospital, your doctor may ask you to continue to take 1 subcutaneous injection every day for up to 4 weeks.

Medical Patients: while you are in the hospital, your doctor or a nurse will give you 1 subcutaneous injection once a day. The usual duration of administration is 6 to 11 days.

Treatment of Deep Vein Thrombosis, with or without Embolism: while you are in the hospital, your doctor or a nurse will give you 1 subcutaneous injection once or twice daily for about 10 days.

Treatment of Unstable Angina or Non-Q-Wave Myocardial Infarction: while you are in the hospital, your doctor or a nurse will give you 2 subcutaneous injections every day (one injection every 12 hours) along with oral ASA (100 to 325 mg once daily) for a minimum of 2 days.

Treatment of acute ST-segment Elevation Myocardial Infarction (STEMI): while you are in the hospital, your doctor or a nurse will give you a single intravenous (IV) injection followed by 2 subcutaneous injections every day (one injection every 12 hours) along with oral ASA (75 to 325 mg once daily) for a minimum of 8 days, unless contraindicated.

It is possible that after you go home, you may need to continue your injections of REDESCA HP for a few days.

Prevention of thrombus formation in the extracorporeal circulation during hemodialysis: while you are in the hospital, your doctor or a nurse will inject REDESCA HP into the arterial line of the circuit at the beginning of the dialysis session. The effect of this dose is usually sufficient for a 4-hour session.

#### Overdose:

Accidental overdosage may result in hemorrhaging, which cannot be treated at home. Therefore, if you suspect that you have used too much REDESCA HP, call your doctor immediately even if you do not yet observe any unusual symptoms. Your doctor can then make arrangements to bring you to hospital for observation and/or treatment.

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

#### Missed dose:

If you miss a dose of this medication by a few hours, take it as soon as you remember. However if you are close to the time of the next dose, skip the missed dose and proceed with the regular dosing schedule. Do not double doses. If you are unsure about how to proceed contact your doctor or your pharmacist.

#### What are possible side effects from using REDESCA HP?

These are not all the possible side effects you may feel when taking REDESCA HP. If you experience any side effects not listed here, tell your healthcare professional.

Administration of REDESCA HP may result in bleeding which can have serious or life-threatening consequences. Hemorrhagic strokes (bleeding inside of the brain) and serious intra-abdominal bleeding (bleeding into the body cavity below diaphragm which contains stomach, intestines, liver, and other organs) have been reported. REDESCA HP is generally well tolerated when used according to directions of use, nevertheless e.g. hair loss could occur. Long term use of REDESCA HP (greater than 3 months) may increase the risk of bone thinning (osteoporosis).

| Serious side effects and what to do about them                                              |                                      |              |                                                 |
|---------------------------------------------------------------------------------------------|--------------------------------------|--------------|-------------------------------------------------|
| Symptom / effect                                                                            | Talk to your healthcare professional |              | Stop taking drug and get immediate medical help |
|                                                                                             | Only if severe                       | In all cases |                                                 |
| <b>VERY COMMON</b>                                                                          |                                      |              |                                                 |
| Bleeding (e.g. at site injection, nosebleeds, blood in urine, bloody stools, bleeding gums) |                                      |              | ✓                                               |
| Changes in the results of blood tests done to check your liver                              |                                      | ✓            |                                                 |
| <b>COMMON</b>                                                                               |                                      |              |                                                 |
| Headache                                                                                    | ✓                                    |              |                                                 |
| Purplish or reddish discolouration or pain around the injection site                        | ✓                                    |              |                                                 |

| Serious side effects and what to do about them                                                                                                                                      |                                      |              |                                                 |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------|--------------|-------------------------------------------------|
| Symptom / effect                                                                                                                                                                    | Talk to your healthcare professional |              | Stop taking drug and get immediate medical help |
|                                                                                                                                                                                     | Only if severe                       | In all cases |                                                 |
| Spontaneous bruising (a bruise not caused by a blow or any apparent reason)                                                                                                         |                                      | ✓            |                                                 |
| <b>UNCOMMON</b><br>Abdominal pain                                                                                                                                                   |                                      | ✓            |                                                 |
| Signs of liver problems such as loss of appetite, dark urine, light-colored stools, yellowing of the skin or eyes (jaundice)                                                        |                                      | ✓            |                                                 |
| <b>RARE</b><br>Allergic reaction skin rash, angioedema (swelling of lips, face, throat and tongue, breathing difficulties) and anaphylactic/anaphylactoid reactions including shock |                                      |              | ✓                                               |
| Problems in controlling your bowels and/or bladder                                                                                                                                  |                                      | ✓            |                                                 |
| Tingling, numbness and muscular weakness (particularly in the lower part of your body) when you have had a spinal puncture or a spinal anaesthetic                                  |                                      |              | ✓                                               |
| <b>UNKNOWN</b><br>Chest pain or shortness of breath                                                                                                                                 |                                      |              | ✓                                               |
| Confusion                                                                                                                                                                           |                                      | ✓            |                                                 |
| Dizziness                                                                                                                                                                           |                                      | ✓            |                                                 |
| Pain or swelling in any part of your leg, foot or hip                                                                                                                               |                                      | ✓            |                                                 |
| Rapid or unusual heart beat                                                                                                                                                         |                                      |              | ✓                                               |
| Skin discolouration as caused by ruptured blood vessels                                                                                                                             |                                      | ✓            |                                                 |
| Vomiting                                                                                                                                                                            |                                      | ✓            |                                                 |

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

#### **Reporting Side Effects**

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

*NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

#### **Storage:**

Store below 25 C. Do NOT freeze.

Keep out of the reach and sight of children.

#### **If you want more information about REDESCA HP:**

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer's website ([www.valeopharma.com](http://www.valeopharma.com)), or by calling 1-855-694-0151.

#### **Instructions for use:**

**Instructions for self-injection of REDESCA HP.** Your doctor may want you to continue your REDESCA HP injections at home for a few days. **If so, he or a nurse will show you how to administer your REDESCA HP injections before you are released from hospital. It is essential that you follow these instructions exactly. If you have questions, be sure you ask your doctor or nurse to provide the explanations you require.**

Proper subcutaneous (under the skin) injection of REDESCA HP is essential to prevent pain and bruising at the injection site.

When at home, there is nothing for you to prepare. The syringe is pre-filled with the exact amount of drug required. Do not press on the plunger prior to injection.

REDESCA HP solution should be inspected visually for clarity, particulate matter, precipitation, discolouration, and leakage prior to administration. Do not use if solution shows haziness, particulate matter, discolouration or leakage.

The recommended site for injection is into the fat of the lower abdomen. This should be at least 5 centimeters away from your belly button and out towards your sides.

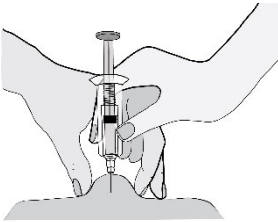
Prior to injection, wash your hands and cleanse (do not rub) the selected site for injection with an alcohol swab. Select a different site of the lower abdomen for each injection.

Carefully pull off the needle cap from the syringe. Throw away the cap. The syringe is pre-filled and ready to use.

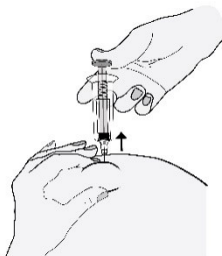


DO NOT press on the plunger before injecting yourself to get rid of air bubbles. This can lead to a loss of the medicine. Once you have removed the cap, do not allow the needle to touch anything. This is to make sure the needle stays clean (sterile).

- Sit or lie down in a comfortable position and gather a fold of skin with your thumb and forefinger.
- Hold the syringe in the hand you write with (like a pencil) and with your other hand, gently pinch the cleaned area of your abdomen between your forefinger and thumb to make a fold in the skin.
- Make sure you hold the skin fold throughout the injection.
- Hold the syringe so that the needle is pointing downwards (vertically at a 90° angle). Insert the full length of the needle into the skin fold.

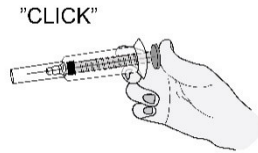


- Press down on the plunger with your finger. This will send the medicine into the fatty tissue of the stomach. Make sure you hold the skin fold throughout the injection.
- Remove the needle by pulling it straight out. Do not release the pressure on the plunger.



**To avoid bruising, do not rub the injection site after you have injected yourself.**

- Push hard on the plunger. The protective sleeve, which is in the form of a plastic cylinder, will be activated automatically and it will completely cover the needle.



- You should then safely dispose of the syringe and needle with its protective sleeve, so they remain out of reach of children.

This leaflet was prepared by Shenzhen Techdow Pharmaceutical Co., Ltd.

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