doses of Enoxaparin Injection was employed. The incidence of bleeding complications was higher in elderly patients as compared to younger patients when Enoxaparin Injection was administered at doses of 1.5 mg/kg once a day or 1 mg/kg every 12 hours.

**SIDE EFFECTS**

**Hemorrhage:** The incidence of major hemorrhagic complications during Enoxaparin Injection treatment has been low.

**Liver:** Transient, asymptomatic elevations of liver transaminases to greater than three times the upper limit of normal LMWH and Heparin unfractioned.

**Hypersensitivity:** Thrombocytopenia, allergic reactions are rare but occur with Low molecular weight Heparin, anaphylactic reactions to unfractionated & Low molecular weight Heparin have been observed rarely.

**Local Reactions:** Mild local irritation, pain, hematoma, ecchymosis, and erythema may follow subcutaneous injection of Enoxaparin Injection.

**DRUG INTERACTIONS**

Unless really needed, agents which may enhance the risk of hemorrhage should be discontinued prior to initiation of Enoxaparin Injection therapy. These agents include medications such as: anticoagulants, platelet inhibitors including acetylsalicylic acid, salicylates, NSAIDs, dipyridamole, or sulfinpyrazone. If co-administration is essential, conduct close clinical and laboratory monitoring.

**STABILITY**

Use Multi Dose vial within 7 days of opening the vial

**WARNINGS**

Enoxaparin Injection is not intended for intramuscular administration. Enoxaparin Injection cannot be used interchangeably with heparin or other low molecular weight heparins as they differ in manufacturing process, molecular weight distribution, anti-Xa and anti-IIa activities, units, and dosage.

**Enoxaparin Injection should be used with extreme caution in patients with a history of heparin-induced thrombocytopenia.**

**PRESENTATION**

**BIO-ENOX®** is available in pre-filled syringe as
**BIO-ENOX®** 20 mg
**BIO-ENOX®** 40 mg
**BIO-ENOX®** 60 mg
**BIO-ENOX®** 80 mg

**BIO-ENOX®** 100 mg/mL (5 mL Multi Dose Vial)

**STORAGE**

Store at 25°C or below. DO NOT FREEZE.

**Keep out of the reach of children.**

*Manufactured & Marketed by*

Bharat Biotech
Genome Valley, Hyderabad-500 078. A.P. India.

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For use by a Registered Medical Practitioner or Hospital or Laboratory only

℞

# Enoxaparin Sodium Injection I.P.
## Low Molecular Weight Heparin

**BIO-ENOX®**
बायो-एनोक्स®

(20 mg / 40 mg / 60 mg / 80 mg in Pre-filled Syringe)
(500 mg/5mL in 5 mL Multi dose Vial)

**DESCRIPTION**

**BIO-ENOX®** Injection is a sterile aqueous solution containing enoxaparin sodium, a low molecular weight heparin which has antithrombotic properties.

**COMPOSITION**

Available in 20 mg, 40 mg, 60 mg and 80 mg Pre-filled syringes and 500 mg/5 mL in 5 mL Multi Dose vial

**BIO-ENOX®** (PFS) 20 mg/0.2 mL (2,000 anti-Xa I.U/0.2mL)

| | | |
|---|---|---|
| Enoxaparin Sodium | I.P. | 20 mg |
| Water for Injection | I.P. | 0.2 mL |

**BIO-ENOX®** (PFS) 40 mg/0.4 mL (4,000 anti-Xa I.U/0.4mL)

| | | |
|---|---|---|
| Enoxaparin Sodium | I.P. | 40 mg |
| Water for Injection | I.P. | 0.4 mL |

**BIO-ENOX®** (PFS) 60 mg/0.6 mL (6,000 anti-Xa I.U/0.6mL)

| | | |
|---|---|---|
| Enoxaparin Sodium | I.P. | 60 mg |
| Water for Injection | I.P. | 0.6 mL |

**BIO-ENOX®** (PFS) 80 mg/0.8 mL (8,000 anti-Xa I.U/0.8mL)

| | | |
|---|---|---|
| Enoxaparin Sodium | I.P. | 80 mg |
| Water for Injection | I.P. | 0.8 mL |

**BIO-ENOX®** 5 mL Multi Dose Vial 500 mg/5mL
Each ml contains

| | | |
|---|---|---|
| Enoxaparin Sodium | I.P. | 100mg(10,000 anti-Xa IU) |
| Benzyl Alcohol | I.P. | 15mg(as preservative) |
| Water for Injection | I.P | q. s to 1 mL |

**INDICATIONS**

**BIO-ENOX®** is indicated for, prophylaxis of deep vein thrombosis which may lead to pulmonary embolism, in patients undergoing abdominal surgery who are at risk for thromboembolic complications, in patients undergoing hip replacement surgery, in patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness, polytrauma, arterial thrombosis, medical conditions e.g stroke and cancer / catheter related thrombosis and for prophylaxis of thrombus formation in the extracorporeal circulation during haemodialysis.

**DOSAGE AND ADMINISTRATION**

*Treatment of Deep Vein Thrombosis with or without Pulmonary Embolism*
For patients with acute deep vein thrombosis without pulmonary embolism, the recommended dose of **BIO-ENOX®** Injection is 1 mg/kg every 12 hours, administered Subcutaneous. For patients with acute deep vein thrombosis with pulmonary embolism or patients with acute deep vein thrombosis without pulmonary embolism, the recommended dose of **BIO-ENOX®** Injection is 1 mg/kg every 12 hours administered Subcutaneous or 1.5 mg/kg once a day administered Subcutaneous at the same time every day. **BIO-ENOX®** Injection should be continued for a minimum of 5 days and until a therapeutic oral anticoagulant effect has been achieved. The average duration of administration is 7 days.

*Abdominal Surgery:* 40 mg once a day administered by subcutaneous injection with the initial dose given 2 hours prior to surgery and administered for 7 to 10 days.

*Hip or Knee Replacement Surgery:* 30 mg 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 and administered for 7 to 10 days.

*Unstable Angina and Non-Q-Wave Myocardial Infarction:* 1 mg/kg administered subcutaneous every 12 hours in conjunction with oral aspirin therapy (100 to 325 mg once daily) and should be taken for a minimum of 2 days and continued until clinical stabilization. To minimize the risk of bleeding following vascular instrumentation, adhere precisely to the intervals recommended between **BIO-ENOX®** doses. *For prophylaxis of thrombus formation in the extracorporeal circulation during haemodialysis*

A dose equivalent to 1 mg/kg (100 IU/kg) introduced into the arterial line at the beginning of a dialysis session is usually sufficient for a 4 hour session. If fibrin rings are found, longer than normal session, a further dose of 0.5 to 1mg/kg may be given. For patients at a high risk of hemorrhage the dose should be reduced to 0.5 mg/kg for double vascular access or 0.75 mg/kg (75 IU/kg) for single vascular access.

**CLINICAL PHARMACOLOGY**

Enoxaparin is a low molecular weight heparin with antithrombotic properties. In humans, enoxaparin given at a dose of 1.5 mg/kg subcutaneously is characterized by a higher ratio of anti-Factor Xa to anti-Factor IIa activity.

**Pharmacokinetics**

*Absorption:* Maximum anti-Factor Xa and anti-thrombin (anti-Factor IIa) activities occur 3 to 5 hours after subcutaneous injection of enoxaparin. Mean peak anti-Factor Xa activity was 0.16 IU/mL (1.58 µg/mL) and 0.38 IU/ml (3.83 µg/mL) after the 20 mg and 40 mg clinically tested subcutaneous doses, respectively. Mean (n = 46) peak anti-Factor Xa activity was 1.1 IU/mL at steady state in patients with unstable angina receiving 1mg/kg SC every 12 hours for 14 days. Mean absolute bioavailability of enoxaparin, after 1.5 mg/kg given SC, based on anti-Factor Xa activity is approximately 100% in healthy volunteers. After repeated subcutaneous administration of 40 mg once daily and 1.5 mg/kg once-daily regimens in healthy volunteers, the steady state is reached on day 2 with an average exposure ratio about 15% higher than after a single dose. Steady-state enoxaparin activity levels are well predicted by single-dose pharmacokinetics. After repeated subcutaneous administration of 1 mg/kg twice daily regimen, the steady state is reached from day 4 with mean exposure about 65% higher than after a single dose and mean peak and trough levels of about 1.2 and 0.52 IU/mL, respectively. Based on enoxaparin sodium pharmacokinetics, this difference in steady state is expected and within the therapeutic range.

*Elimination:* Following intravenous dosing, the total body clearance of enoxaparin is 26 ml/min. Elimination half-life based on anti-Factor Xa activity was 4.5 hours after a single subcutaneous dose to about 7 hours after repeated dosing. Following a 40 mg subcutaneous once a day dose, significant anti-Factor Xa activity persists in plasma for about 12 hours.

*Metabolism:* Enoxaparin sodium is primarily metabolized in the liver by desulfation and/or depolymerization to lower molecular weight species with much reduced biological potency. 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.

**OVERDOSE**

**Symptoms/Treatment:** Overdosage following administration of Enoxaparin Injection may lead to hemorrhagic complications. Injected Enoxaparin Injection may be largely neutralized by equal amounts of slow I.V. injection of 1% protamine sulfate. After 12 hours of the enoxaparin sodium injection, protamine administration may not be required. 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 techniques and treatment of anaphylactic shock are readily available.

**CONTRAINDICATIONS**

Enoxaparin is contraindicated in patients with bleeding disorders, active major bleeding, thrombocytopenia associated with a positive test for anti-platelet antibody and platelet defects or in patients with hypersensitivity to enoxaparin sodium and severe untreated hypertension. Patients with known hypersensitivity to heparin or pork products should not be treated with Enoxaparin.

**PRECAUTIONS**

Enoxaparin injection procedure should be observed carefully. It is recommended that the platelet count be measured before the initiation of the treatment and regularly thereafter during treatment. Enoxaparin should be used with caution in case of renal or hepatic insufficiency, history of peptic ulcer or any organic lesion likely to bleed, hemorrhagic vascular cerebral stroke, uncontrolled severe arterial hypertension, diabetic retinopathy, injuries and operation to brain, spinal cord, eyes & ears.

*Mechanical Prosthetic Heart Valves*
Use of Enoxaparin has not been adequately studied for thromboprophylaxis in patients with mechanical prosthetic heart valves and has not been adequately studied for long-term use in this patient population. Pregnant women with mechanical prosthetic heart valves may be at higher risk for thromboembolism.

*Renal Impairment*
Patients with renal impairment (severe mean creatinine clearance < 11.4 mL/min) are prone to an increased exposure to enoxaparin sodium and should be observed carefully for signs & symptoms of bleeding. Hence a dosage adjustment is recommended for therapeutic and prophylactic dosage ranges. No dosage adjustment is recommended in patients with moderate and mild renal impairment.

*Carcinogenesis, Mutagenesis, Impairment of Fertility*
Enoxaparin was not mutagenic in *in vitro* tests, including the Ames test, mouse lymphoma cell forward mutation test, and human lymphocyte chromosomal aberration test, and the in vivo rat bone marrow chromosomal aberration test.

*Pregnancy*
All pregnancies have a background risk of birth defects, loss, or other adverse outcome regardless of drug exposure. Enoxaparin is not predicted to increase the risk of developmental abnormalities. Enoxaparin does not cross the placenta, based on human and animal studies and shows no evidence of teratogenic effects or fetotoxicity.

**Pediatric Use**
Safety and effectiveness of Enoxaparin Injection in pediatric patients have not been established.

**Nursing Mothers**
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Enoxaparin Injection is administered to nursing women.

**Geriatric Use**
Efficacy of Enoxaparin Injection in the elderly was similar to that seen in younger patients. The incidence of bleeding complications was similar between elderly and younger patients when 30 mg every 12 hours or 40 mg once a day

Size: 130 mm x 200 mm
Front & Back Middle single fold

Date : 14-12-2010

| Specifications | Product | Size | Strength | Paper | GSM | Fold | Colours CMYK / Pantone |
|---|---|---|---|---|---|---|---|
| | BIO-ENOX® | 130 x 200 mm | | | 60 | | |
| **Approvals** | **CRA** | **Q C** | **Q A** | **Marketing** | **Exports** | **Production** | Black 90% |
| | | | | | | | |
| Bharat Biotech INTERNATIONAL LIMITED — Genome Valley, Shameerpet, Hyderabad - 500 078. A.P. India. Tel.: +91 40 2348 0567 Fax: +91 40 2348 0560 www.bharatbiotech.com | | | | **Purchase (For Receipt)** | | | |