Lovenox®
(enoxaparin) Injection

IN-1107 Rev. 1/93

Lovenox® (enoxaparin) Injection

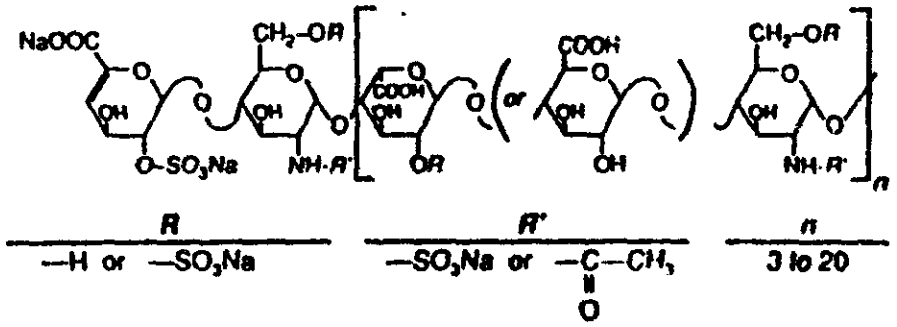
DESCRIPTION

Enoxaparin is a sterile, low molecular weight heparin for injection. Each syringe contains 30 mg enoxaparin in 0.3 mL Water for Injection. The approximate anti-Factor Xa activity per syringe is 3000 IU (with reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard). Nitrogen is used in the headspace to inhibit oxidation. The pH of the injection is 5.5-7.5. The solution is preservative-free and intended for use only as a single-dose injection.

Enoxaparin is obtained by alkaline degradation of heparin benzyl ester derived from porcine intestinal mucosa. Its structure is characterized by a 2-O-sulfo-4-enepyranosuronic acid group at the non-reducing end and a 2-N,6-O-disulfo-D-glucosamine at the reducing end of the chain. The substance is the sodium salt. The average molecular weight is about 4500. The molecular weight distribution is:

<2000 daltons	≤ 20%
2000 to 8000 daltons	≥ 68%
>8000 daltons	≤ 18%

STRUCTURAL FORMULA



R	R'	n
—H or —SO_3Na	—SO_3Na or —C(=O)—CH_3	3 to 20

CLINICAL PHARMACOLOGY

Enoxaparin is a low molecular weight heparin which has antithrombotic properties. In man enoxaparin is characterized by a higher ratio of anti-Factor Xa to anti-Factor IIa activity (3.35 ± 0.89) than unfractionated heparin (1.22 ± 0.13). Following the administration of a single subcutaneous dose of up to 90 mg of enoxaparin to healthy subjects, no appreciable change was observed in fibrinogen level and other parameters of fibrinolysis. At the recommended doses, single injections of enoxaparin do not significantly influence platelet aggregation or affect global clotting tests (i.e. prothrombin time (PT) or activated partial thromboplastin time (APTT)).

Pharmacodynamics

Maximum anti-Factor Xa and antithrombin (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 0.36 IU/mL (3.83 µg/mL) after the 20 mg and the 40 mg clinically tested doses, respectively. Mean absolute bioavailability of enoxaparin based on anti-Factor Xa activity is 92% in healthy volunteers. The volume of distribution of anti-Factor Xa activity is about 5 L. Following i.v. dosing, the total body clearance of enoxaparin is 25 mL/min. Elimination half-life based on anti-Factor Xa activity was about 4.5 hours after subcutaneous administration. Following a 40 mg dose significant anti-Factor Xa activity persists in plasma for about 12 hours. There appears to be no appreciable increase in anti-Factor Xa activity after dosing for 3 days in young healthy subjects. Clearance, C_{max}, and AUC for anti-Factor Xa values following single and multiple s.c. dosing in elderly subjects and subjects with renal failure were close to those observed in normal subjects. An increase of 25% in the area under anti-Factor Xa activity versus time curve was observed following once daily dosing in healthy elderly subjects for 10 days. The kinetics of anti-Factor Xa activity in aortic patients undergoing dialysis are similar to those in normal subjects following i.v. dosing.

The decline of anti-Factor Xa activity with time was parallel to the decay curve of plasma total radioactivity (^{99m}Tc) in healthy volunteers. Following intravenous dosing of enoxaparin labeled with the gamma-emitter, ^{99m}Tc, 40% of radioactivity and 6-20% of anti-Factor Xa activity were recovered in urine in 24 hours.

CLINICAL TRIALS

Lovenox has been shown to prevent postoperative deep vein thrombosis (DVT) following hip replacement surgery. The data from two controlled clinical trials are summarized in the following tables. In all studies, efficacy is based on "all treated patients" analysis.

In a double-blind study, Lovenox 30 mg q12h sc was compared to placebo. Treatment was initiated within 12-24 hours post-surgery and was continued for 10-14 days post-operatively.

	Treatment Group	
Treatment Group Dosing Regimen	Lovenox 30 mg q12h n (%)	Placebo q12h n (%)
All Treated Patients	50 (100%)	50 (100%)
Treatment Failures		
Total DVT (%)	5 (10%)	23 (46%)*
Proximal DVT (%)	1 (2%)	11 (22%)**

*p value versus placebo = 0.0002
**p value versus placebo = 0.0134

A double blind, multicenter study compared three dosing regimens of Lovenox. Treatment was initiated within two days post-surgery and was continued for up to 7 days post-operatively.

	Treatment Group		
		Lovenox	
Dose	10 mg QD n (%)	30 mg q12h n (%)	40 mg QD n (%)
All Treated Patients	161 (100%)	208 (100%)	199 (100%)
Treatment Failures			
Total DVT (%)	40 (25%)	22 (11%)*	27 (14%)**
Proximal DVT (%)	17 (11%)	8 (4%)	9 (5%)

*p value versus Lovenox 10 mg QD = 0.0008
**p value versus Lovenox 10 mg QD = 0.0168
There was no significant difference between the 30 mg BID and 40 mg QD regimens.

INDICATION AND USAGE

~~Lovenox (enoxaparin) injection is indicated for the prevention of deep vein thrombosis and pulmonary embolism following hip replacement surgery.~~

Lovenox injection is indicated for the prevention of deep vein thrombosis, which may lead to pulmonary embolism, following hip replacement surgery.

CONTRAINDICATIONS

Lovenox injection is contraindicated in patients with active major bleeding, in patients with thrombocytopenia associated with a positive *in vitro* test for anti-platelet antibody in the presence of Lovenox injection, or in patients with hypersensitivity to Lovenox injection.

Patients with known hypersensitivity to heparin or pork products should not be treated with enoxaparin.

WARNINGS

Lovenox injection is not intended for intramuscular administration.

Lovenox cannot be used interchangeably (unit for unit) with unfractionated heparin or other low molecular weight heparins.

Lovenox should be used with extreme caution in patients with history of heparin-induced thrombocytopenia.

Hemorrhage:

Lovenox injection like other anticoagulants, should be used with extreme caution in conditions with increased risk of hemorrhage, such as bacterial endocarditis, congenital or acquired bleeding disorders, active ulceration and angiodysplastic gastrointestinal disease, hemorrhagic stroke or shortly after brain, spinal or ophthalmological surgery.

Bleeding can occur at any site during therapy with enoxaparin. *An unexplained fall in hematocrit or blood pressure should lead to a search for a bleeding site.*

Thrombocytopenia:

Moderate thrombocytopenia (platelet counts <100,000/mm^3 and > 50,000/mm^3) occurred at a rate of about 2% in patients given Lovenox, 3% in patients given heparin, and 0% in patients receiving placebo in clinical trials. Thrombocytopenia of any degree should be monitored closely.

PRECAUTIONS

General

Lovenox injection should not be mixed with other injections or infusions. Lovenox injection should be used with care in patients with a bleeding diathesis, uncontrolled arterial hypertension or a history of recent gastrointestinal ulceration and hemorrhage. Elderly patients and patients with renal insufficiency may show delayed elimination of enoxaparin. Enoxaparin should be used with care in these patients.

If thromboembolic events occur despite enoxaparin prophylaxis, Lovenox should be discontinued and appropriate therapy initiated.

Laboratory Tests:

Periodic complete blood counts, including platelet count, and stool occult blood tests are recommended during the course of treatment with Lovenox injection.

Drug Interactions:

Lovenox injection should be used with care in patients receiving oral anticoagulants, and/or platelet inhibitors.

Drug/Laboratory Test Interactions:

Elevations of Serum Transaminases

Asymptomatic increases in transaminase levels (SGOT [AST] and SGPT [ALT]) greater than three times the upper limit of normal of the laboratory reference range have been reported in 2 of 10 normal subjects and in up to 5% of patients during treatment with Lovenox Injection. Similar significant increases in transaminase levels have also been observed in patients and normal volunteers treated with heparin and other low molecular weight heparins. Such elevations are fully reversible and are rarely associated with increases in bilirubin. Since transaminase determinations are important in the differential diagnosis of myocardial infarction, liver disease and pulmonary emboli, elevations that might be caused by drugs like Lovenox should be interpreted with caution.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

No long-term studies in animals have been performed to evaluate carcinogenic potential of enoxaparin. 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. Enoxaparin was found to have no effect on fertility or reproductive performance of male and female rats at subcutaneous doses up to 20 mg/kg/day or 141 mg/m^2/day. The maximum received human dose in clinical trials was 1.5 mg/kg/day or 48.4 mg/m^2/day.

Pregnancy: Teratogenic Effects

Pregnancy category B: Teratology studies have been conducted in rats and rabbits at subcutaneous doses of enoxaparin up to 30 mg/kg/day or 211 mg/m^2/day and 410 mg/m^2/day, respectively. The maximum received human dose in clinical trials was 1.5 mg/kg/day or 48.4 mg/m^2/day. There was no evidence of teratogenic effects or fetotoxicity due to enoxaparin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

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 is administered to nursing women.

Pediatric Use:

Safety and effectiveness of enoxaparin in children has not been established.

ADVERSE REACTIONS

Hemorrhage:

The incidence of hemorrhagic complications during Lovenox ® injection treatment has been low.

The following rates of major bleeding events have been reported during clinical trials with Lovenox injection and heparin and placebo in patients undergoing hip replacement surgery.

	Major Bleeding Episode*	
Enoxaparin	Heparin	Placebo
30 mg q12h	15000 U/24h	
n = 788	n = 541	n = 50
31 (4%)	32 (6%)	2 (4%)

*Bleeding complication considered major if accompanied by a significant clinical event or if hemoglobin decreased by ≥ 2 g/dL or transfusion of 2 or more units of blood products was required.

Thrombocytopenia:

During clinical trials with Lovenox Injection, moderate thrombocytopenia, defined as a platelet count less than 100,000/mm^3, was reported in 2% of patients given Lovenox, 3% in patients given heparin and 6% in patients receiving placebo (see WARNINGS).

Local Irritation:

Mild local irritation, pain, hematoma and erythema may follow subcutaneous injection of Lovenox Injection.

Other:

Other adverse effects that were thought to be possibly or probably related to treatment with Lovenox Injection, heparin or placebo in clinical trials, and that occurred at a rate of at least 2% in the enoxaparin group, are shown below.

Adverse Events Occurring at ≥ 2% Incidence in Enoxaparin Treated Patients (Excluding Unrelated Adverse Events)

	Enoxaparin 30 mg q12h n = 788		Heparin 15000 U/24h n = 541		Placebo n = 50	
Adverse Event	Severe	Total	Severe	Total	Severe	Total
Fever	<1%	4%	<1%	3%	0%	4%
Pain	<1%	2%	1%	3%	0%	8%
Hemorrhage	<1%	5%	<1%	5%	0%	2%
Nausea	<1%	3%	<1%	2%	0%	2%
Ecchymosis	<1%	2%	<1%	2%	0%	2%
Hypochromic anemia	1%	3%	3%	7%	2%	16%
Edema	1%	3%	<1%	2%	0%	4%
Peripheral edema	1%	3%	1%	5%	0%	0%
Confusion	<1%	2%	<1%	1%	0%	0%

OVERDOSAGE:

SYMPTOMS/TREATMENT:

Accidental overdosage following administration of Lovenox Injection may lead to hemorrhagic complications. This

may be largely neutralized by the slow intravenous injection of protamine sulfate (1% solution). The dose of protamine sulfate should be equal to the dose of Lovenox injection injected: 1 mg protamine sulfate should be administered to neutralize 1 mg Lovenox injection. A second infusion of 0.5 mg/mg protamine sulfate may be administered if the APTT measured 2 to 4 hours after the first infusion remains prolonged. However, even with higher doses of protamine, the APTT may remain more prolonged than under normal conditions found following administration of conventional heparin. In all cases, the anti-Factor Xa activity is never completely neutralized (maximum about 60%). 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. For additional information consult the labeling of Protamine Sulfate Injection, USP, products.

A single subcutaneous dose of 46.4 mg/kg enoxaparin was lethal to rats. The symptoms of acute toxicity were ataxia, decreased motility, dyspnea, cyanosis and coma.

DOSAGE AND ADMINISTRATION

Adult Dosage:

In patients undergoing hip replacement, the recommended dose of Lovenox injection is 30 mg twice daily administered by subcutaneous injection with the initial dose given as soon as possible after surgery, but not more than 24 hours post-operatively. Treatment should be continued throughout the period of post-operative care until the risk of deep vein thrombosis has diminished. Up to 14 days administration has been well tolerated in controlled clinical trials. The average duration of administration is 7 to 10 days.

All patients should be screened prior to prophylactic administration of Lovenox to rule out a bleeding disorder. There is usually no need for daily monitoring of the effect of Lovenox in patients with normal preoperative coagulation parameters.

Administration:

Lovenox injection is administered by subcutaneous injection. It must not be administered by intramuscular injection.

Subcutaneous injection technique: Patients should be lying down and Lovenox injection administered by deep subcutaneous injection. Administration should be alternated between the left and right anterolateral and left and right posterolateral abdominal wall. The whole length of the needle should be introduced into a skin fold held between the thumb and forefinger; the skin fold should be held throughout the injection.

Enoxaparin injection is a clear colorless to pale-yellow sterile solution and as with other parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

HOW SUPPLIED

Lovenox injection is available in packs of 10 prefilled syringes. Each Lovenox (enoxaparin) prefilled syringe is affixed with a 26 gauge x ½ inch needle.

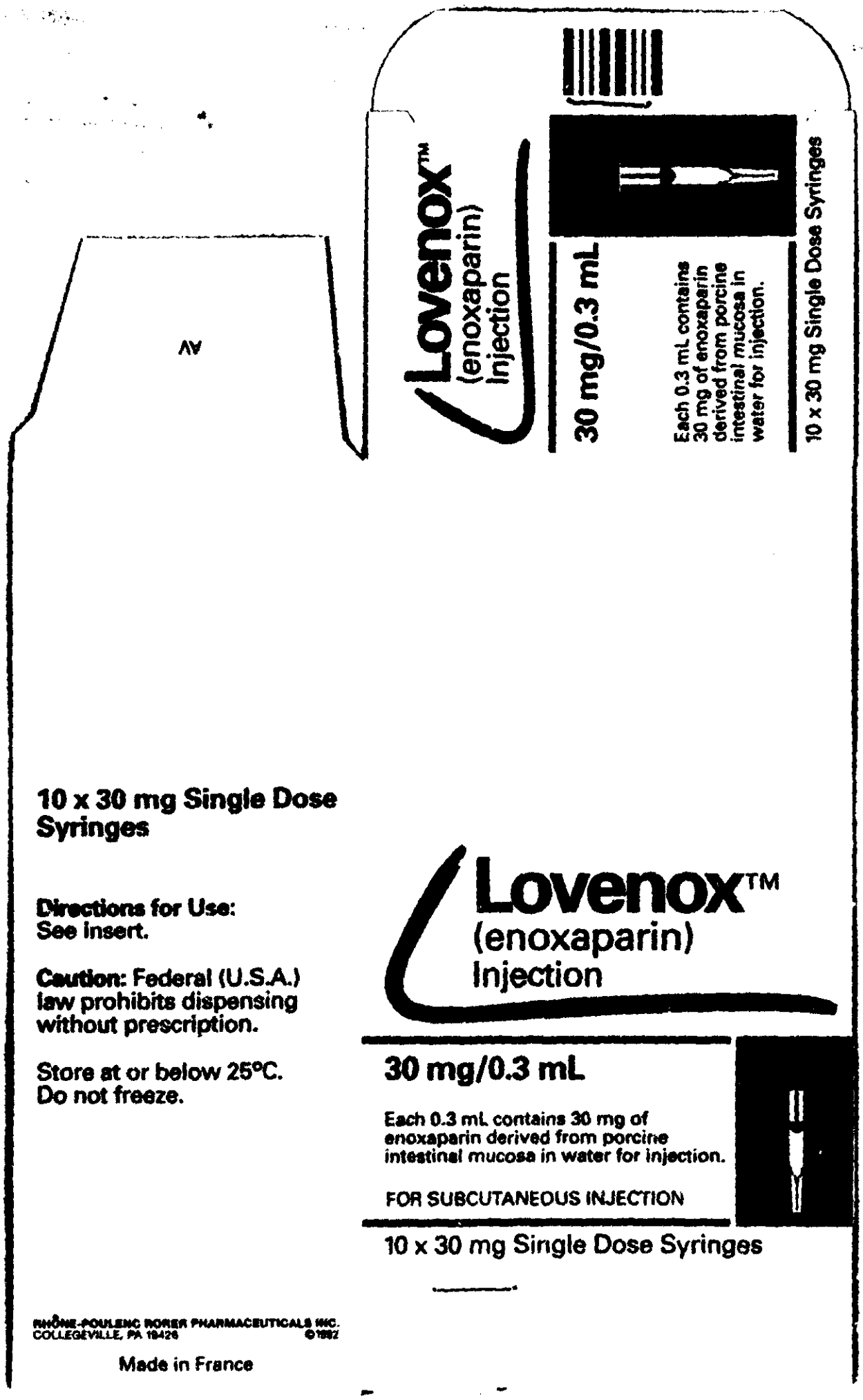
Lovenox contains 30 mg enoxaparin in 0.3 mL of Water for Injection. Lovenox has an anti-Factor Xa activity of approximately 3000 IU (with reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard).

Lovenox injection should be stored at or below 25°C ——— Do not freeze.

Made in France
IN-1107 Rev. 1/93

RHÔNE-POULENC RORER PHARMACEUTICALS INC.
COLLEGEVILLE, PA 19426

10 x 30 mg Single Dose syringes Carton



Blister Pack Label

Lovenox™
(enoxaparin) Injection
30 mg/0.3 mL

Each 0.3 mL contains 30 mg of enoxaparin derived from porcine intestinal mucosa in water for injection. See insert for directions for use.
FOR SUBCUTANEOUS INJECTION. Caution: Federal (U.S.A.) law prohibits dispensing without prescription. Store at or below 25°C. Do not freeze.

NDC 0075-[illegible]
1 Single Dose Prefilled Syringe — 0.3 mL
Made in France
[illegible]
PHARMACEUTICALS INC.
COLLEGEVILLE, PA [illegible]
MP-1183

Prefilled Syringe Label