

Chinese Study Finds No Blood Pressure J-Curve

BY BRUCE JANCIN
Denver Bureau

SAN ANTONIO — Among patients with known cardiovascular disease there is no J-shaped association between blood pressure and either future cardiovascular events or all-cause mortality, according to data from the China National Hypertension Survey Epidemiology Study.

“These data indicate there is a strong, independent, and direct association between

blood pressure and mortality among men and women with a history of cardiovascular disease. Furthermore, our findings support a lower blood pressure achievement goal among patients with cardiovascular disease in order to reduce mortality,” Dr. Jing Chen said at a meeting of the American Heart Association Council for High Blood Pressure Research.

The possible existence of a J-curve—that is, the notion that driving blood pressures lower is beneficial only to a certain

point, after which mortality starts to climb again—has a lengthy history in the field of hypertension. The possibility that it existed in the general population was debated for many years until a consensus emerged that it does not, and that lower is better. More recently the J-curve has been resurrected, with some reports indicating it applies to patients with cardiovascular disease, explained Dr. Chen of Tulane University, New Orleans.

To examine this issue, she turned to the

China National Hypertension Survey Epidemiology Study, which enrolled a nationally representative sample of 158,666 participants aged 15 years or older in 1991. The study included 2,251 men and 1,941 women with a baseline history of coronary heart disease or stroke.

At follow-up during 1999-2000, a direct association was seen between blood pressure and cardiovascular mortality in the subgroup having baseline cardiovascular disease—no J-shaped curve.



Rx only
Brief Summary of Prescribing Information Rev. September 2006

SPINAL / EPIDURAL HEMATOMAS
When neuraxial anesthesia (epidural/spinal anesthesia) or spinal puncture is employed, patients anticoagulated or scheduled to be anticoagulated with low molecular weight heparins or heparinoids for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis. The risk of these events is increased by the use of indwelling epidural catheters for administration of analgesia or by the concomitant use of drugs affecting hemostasis such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, or other anticoagulants. The risk also appears to be increased by traumatic or repeated epidural or spinal puncture. Patients should be frequently monitored for signs and symptoms of neurological impairment. If neurologic compromise is noted, urgent treatment is necessary. The physician should consider the potential benefit versus risk before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis (see also **WARNINGS, Hemorrhage**, and **PRECAUTIONS, Drug Interactions**).

INDICATIONS AND USAGE

Lovenox Injection is indicated for the 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, during and following hospitalization;
- in patients undergoing knee replacement surgery;
- in medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness.

Lovenox Injection is indicated for the prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin.

Lovenox Injection is indicated for:

- the **inpatient treatment** of acute deep vein thrombosis with or without pulmonary embolism, when administered in conjunction with warfarin sodium;
- the **outpatient treatment** of acute deep vein thrombosis without pulmonary embolism when administered in conjunction with warfarin sodium.

See **DOSE AND ADMINISTRATION: Adult Dosage** for appropriate dosage regimens.

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 enoxaparin sodium, or in patients with hypersensitivity to enoxaparin sodium.

Patients with known hypersensitivity to heparin or pork products should not be treated with Lovenox Injection. Patients with known hypersensitivity to benzyl alcohol should not be treated using the multi-dose formulation of Lovenox.

WARNINGS

Lovenox Injection is not intended for intramuscular administration. Lovenox Injection cannot be used interchangeably (unit for unit) 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. Each of these medicines has its own instructions for use.

Lovenox Injection should be used with extreme caution in patients with a 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 ulcerative and angiodysplastic gastrointestinal disease, hemorrhagic stroke, or shortly after brain, spinal, or ophthalmological surgery, or in patients treated concomitantly with platelet inhibitors.

Cases of epidural or spinal hematomas have been reported with the associated use of Lovenox Injection and spinal/epidural anesthesia or spinal puncture resulting in long-term or permanent paralysis. The risk of these events is higher with the use of post-operative indwelling epidural catheters or by the concomitant use of additional drugs affecting hemostasis such as NSAIDs (see boxed WARNING; ADVERSE REACTIONS, Ongoing Safety Surveillance; and PRECAUTIONS, Drug Interactions).

Major hemorrhages including retroperitoneal and intracranial bleeding have been reported. Some of these cases have been fatal. Bleeding can occur at any site during therapy with Lovenox Injection. An unexplained fall in hematocrit or blood pressure should lead to a search for a bleeding site.

Thrombocytopenia:

Thrombocytopenia can occur with the administration of Lovenox Injection. Moderate thrombocytopenia (platelet counts between 100,000/mm³ and 50,000/mm³) occurred at a rate of 1.3% in patients given Lovenox Injection, 1.2% in patients given heparin, and 0.7% in patients given placebo in clinical trials. Platelet counts less than 50,000/mm³ occurred at a rate of 0.1% in patients given Lovenox Injection, in 0.2% of patients given heparin, and 0.4% of patients given placebo in the same trials.

Thrombocytopenia of any degree should be monitored closely. If the platelet count falls below 100,000/mm³, Lovenox Injection should be discontinued. Cases of heparin-induced thrombocytopenia with thrombosis have also been observed in clinical practice. Some of these cases were complicated by organ infarction, limb ischemia, or death.

Pregnant Women with Mechanical Prosthetic Heart Valves:

The use of Lovenox Injection for thromboprophylaxis in pregnant women with mechanical prosthetic heart valves has not been adequately studied. In a clinical study of pregnant women with mechanical prosthetic heart valves given enoxaparin (1 mg/kg bid) to reduce the risk of thromboembolism, 2 of 8 women developed clots resulting in blockage of the valve and leading to maternal and fetal death. Although a causal relationship has not been established these deaths may have been due to therapeutic failure or inadequate anticoagulation. No patients in the heparin/warfarin group (0 of 4 women) died. There also have been isolated postmarketing reports of valve thrombosis in pregnant women with mechanical prosthetic heart valves while receiving enoxaparin for thromboprophylaxis. Women with mechanical prosthetic heart valves may be at higher risk for thromboembolism during pregnancy, and, when pregnant, have a higher rate of fetal loss from stillbirth, spontaneous abortion and premature delivery. Therefore, frequent monitoring of peak and trough anti-Factor Xa levels, and adjusting of dosage may be needed.

Miscellaneous:

Lovenox multiple-dose vials contain benzyl alcohol as a preservative. The administration of medications containing benzyl alcohol as a preservative to premature neonates has been associated with a fatal “Gasping Syndrome”. Because benzyl alcohol may cross the placenta, Lovenox multiple-dose vials, preserved with benzyl alcohol, should be used with caution in pregnant women and only if clearly needed (see **PRECAUTIONS, Pregnancy**).

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, diabetic retinopathy, and hemorrhage. Lovenox Injection should be used with care in elderly patients who may show delayed elimination of enoxaparin. If thromboembolic events occur despite Lovenox Injection prophylaxis, appropriate therapy should be initiated.

Mechanical Prosthetic Heart Valves:

The use of Lovenox Injection 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. Isolated cases of prosthetic heart valve thrombosis have been reported in patients with mechanical prosthetic heart valves who have received enoxaparin for thromboprophylaxis. Some of these cases were pregnant women in whom thrombosis led to maternal and fetal deaths. Insufficient data, the underlying disease and the possibility of inadequate anticoagulation complicate the evaluation of these cases. Pregnant women with mechanical prosthetic heart valves may be at higher risk for thromboembolism (see **WARNINGS, Pregnant Women with Mechanical Prosthetic Heart Valves**).

Renal Impairment:

In patients with renal impairment, there is an increase in exposure of enoxaparin sodium. All such patients should be observed carefully for signs and symptoms of bleeding. Because exposure of enoxaparin sodium is significantly increased in patients with severe renal impairment (creatinine clearance <30 mL/min), a dosage adjustment is recommended for therapeutic and prophylactic dosage ranges. No dosage adjustment is recommended in patients with moderate (creatinine clearance 30-50 mL/min) and mild (creatinine clearance 50-80 mL/min) renal impairment. (see **DOSE AND ADMINISTRATION** and **CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations**).

Low-Weight Patients:

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). All such patients should be observed carefully for signs and symptoms of bleeding (see **CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations**).

Laboratory Tests:

Periodic complete blood counts, including platelet count, and stool occult blood tests are recommended during the course of treatment with Lovenox Injection. When administered at recommended prophylaxis doses, routine coagulation tests such as Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT) are relatively insensitive measures of Lovenox Injection activity and, therefore, unsuitable for monitoring. Anti-Factor Xa may be used to monitor the anticoagulant effect of Lovenox Injection in patients with significant renal impairment. If during Lovenox Injection therapy abnormal coagulation parameters or bleeding should occur, anti-Factor Xa levels may be used to monitor the anticoagulant effects of Lovenox Injection (see **CLINICAL PHARMACOLOGY: Pharmacokinetics**).

Drug Interactions:

Unless really needed, agents which may enhance the risk of hemorrhage should be discontinued prior to initiation of Lovenox Injection therapy. These agents include medications such as: anticoagulants, platelet inhibitors including acetylsalicylic acid, salicylates, NSAIDs (including ketorolac tromethamine), dipyridamole, or sulfipyrazole. If co-administration is essential, conduct close clinical and laboratory monitoring (see **PRECAUTIONS: Laboratory Tests**).

Carcinogenesis, Mutagenesis, Impairment of Fertility:

No long-term studies in animals have been performed to evaluate the 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 SC doses up to 20 mg/kg/day or 141 mg/m²/day. The maximum human dose in clinical trials was 2.0 mg/kg/day or 78 mg/m²/day (for an average body weight of 70 kg, height of 170 cm, and body surface area of 1.8 m²).

Pregnancy:

Pregnancy Category B: All pregnancies have a background risk of birth defects, loss, or other adverse outcome regardless of drug exposure. The fetal risk summary below describes Lovenox’s potential to increase the risk of developmental abnormalities above background risk.

Fetal Risk Summary:

Lovenox is not predicted to increase the risk of developmental abnormalities. Lovenox does not cross the placenta, based on human and animal studies, and shows no evidence of teratogenic effects or fetotoxicity.

Clinical Considerations:

It is not known if dose adjustment or monitoring of anti-Xa activity of enoxaparin are necessary during pregnancy. Pregnancy alone confers an increased risk for thromboembolism, that is even higher for women with thromboembolic disease and certain high risk pregnancy conditions. While not adequately studied, pregnant women with mechanical prosthetic heart valves may be at even higher risk for thrombosis (see **WARNINGS, Pregnant Women with Mechanical Prosthetic Heart Valves** and **PRECAUTIONS, Mechanical Prosthetic Heart Valves**). Pregnant women with thromboembolic disease, including those with mechanical prosthetic heart valves, and those with inherited or acquired thrombophilias, also have an increased risk of other maternal complications and fetal loss regardless of the type of anticoagulant used.

All patients receiving anticoagulants such as enoxaparin, including pregnant women, are at risk for bleeding. Pregnant women receiving enoxaparin should be carefully monitored for evidence of bleeding or excessive anticoagulation. Consideration for use of a shorter acting anticoagulant should be specifically addressed as delivery approaches (see **BOXED WARNING, SPINAL/EPIDURAL HEMATOMAS**). Hemorrhage can occur at any site and may lead to death of mother and/or fetus. Pregnant women should be apprised of the potential hazard to the fetus and the mother if enoxaparin is administered during pregnancy.

Data:

• **Human Data** - There are no adequate and well-controlled studies in pregnant women. A retrospective study reviewed the records of 604 women who used enoxaparin during pregnancy. A total of 624 pregnancies resulted in 693 live births. There were 72 hemorrhagic events (11 serious) in 63 women. There were 14 cases of neonatal hemorrhage. Major congenital anomalies in live births occurred at rates (2.5%) similar to background rates.

There have been postmarketing reports of fetal death when pregnant women received Lovenox Injection. Causality for these cases has not been determined. Insufficient data, the underlying disease, and the possibility of inadequate anticoagulation complicate the evaluation of these cases.

See WARNINGS: Pregnant Women with Mechanical Prosthetic Heart Valves for a clinical study of pregnant women with mechanical prosthetic heart valves.

• **Animal Data** - Teratology studies have been conducted in pregnant rats and rabbits at SC doses of enoxaparin up to 30 mg/kg/day or 211 mg/m²/day and 410 mg/m²/day, respectively. There was no evidence of teratogenic effects or fetotoxicity due to enoxaparin. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Cases of “Gasping Syndrome” have occurred in premature infants when large amounts of benzyl alcohol have been administered (99-405 mg/kg/day). The multiple-dose vial of Lovenox solution contains 15 mg/1.0 mL benzyl alcohol as a preservative (see **WARNINGS, Miscellaneous**).

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 Lovenox Injection is administered to nursing women.

Pediatric Use:

Safety and effectiveness of Lovenox Injection in pediatric patients have not been established.

Geriatric Use:

Over 2800 patients, 65 years and older, have received Lovenox Injection in pivotal clinical trials. The efficacy of Lovenox Injection in the elderly (≥65 years) was similar to that seen in younger patients (<65 years). The incidence of bleeding complications was similar between elderly and younger patients when 30 mg every 12 hours or 40 mg once a day doses of Lovenox Injection were employed. The incidence of bleeding complications was higher in elderly patients as compared to younger patients when Lovenox Injection was administered at doses of 1.5 mg/kg once a day or 1 mg/kg every 12 hours. The risk of Lovenox Injection-associated bleeding increased with age. Serious adverse events increased with age for patients receiving Lovenox Injection. Other clinical experience (including postmarketing surveillance and literature reports) has not revealed additional differences in the safety of Lovenox Injection between elderly and younger

patients. Careful attention to dosing intervals and concomitant medications (especially antiplatelet medications) is advised. Monitoring of geriatric patients with low body weight (<45 kg) and those predisposed to decreased renal function should be considered (see **CLINICAL PHARMACOLOGY** and **General and Laboratory Tests** subsections of **PRECAUTIONS**).

ADVERSE REACTIONS

Hemorrhage:

The incidence of major 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.

Indications	Major Bleeding Episodes Following Abdominal and Colorectal Surgery ¹		
	Dosing Regimen		
	Lovenox Inj. 40 mg q.d. SC	Lovenox Inj. 30 mg q.12h SC	Heparin 5000 U q8h SC
Abdominal Surgery	n = 555 23 (4%)	n = 560 16 (3%)	n = 674 21 (3%)
Colorectal Surgery	n = 673 28 (4%)	n = 674 21 (3%)	n = 674 21 (3%)

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

Major Bleeding Episodes Following Hip or Knee Replacement Surgery¹

Indications	Major Bleeding Episodes Following Hip or Knee Replacement Surgery ¹		
	Dosing Regimen		
	Lovenox Inj. 40 mg q.d. SC	Lovenox Inj. 30 mg q.12h SC	Heparin 15,000 U/24h SC
Hip Replacement Surgery Without Extended Prophylaxis ²	n = 786 31 (4%)	n = 541 32 (6%)	n = 541 32 (6%)
Hip Replacement Surgery With Extended Prophylaxis	Peri-operative Period ³ n = 288 4 (2%)		
	Extended Prophylaxis Period ⁴ n = 221 0 (0%)		
Knee Replacement Surgery Without Extended Prophylaxis ²	n = 294 3 (1%)	n = 225 3 (1%)	n = 225 3 (1%)

¹ Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease ≥ 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.

² Lovenox Injection 30 mg every 12 hours SC initiated 12 to 24 hours after surgery and continued for up to 14 days after surgery.

³ Lovenox Injection 40 mg SC once a day initiated up to 12 hours prior to surgery and continued for up to 7 days after surgery.

⁴ Lovenox Injection 40 mg SC once a day for up to 21 days after discharge.

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.

Injection site hematomas during the extended prophylaxis period after hip replacement surgery occurred in 9% of the Lovenox Injection patients versus 1.8% of the placebo patients.

Major Bleeding Episodes in Medical Patients With Severely Restricted Mobility During Acute Illness¹

Indications	Major Bleeding Episodes in Medical Patients With Severely Restricted Mobility During Acute Illness ¹		
	Dosing Regimen		
	Lovenox Inj. 20 mg q.d. SC	Lovenox Inj. 40 mg q.d. SC	Placebo ²
Medical Patients During Acute Illness	n = 351 1 (<1%)	n = 360 3 (<1%)	n = 362 2 (<1%)

¹ Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, (2) if the hemorrhage caused a decrease in hemoglobin of ≥ 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.

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

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

Indication	Major Bleeding Episodes in Unstable Angina and Non-Q-Wave Myocardial Infarction		
	Dosing Regimen		
	Lovenox Inj. 1 mg/kg q.12h SC	Lovenox Inj. 1 mg/kg q.12h SC	Heparin aPTT Adjusted i.v. Therapy
Unstable Angina and Non-Q-Wave MI ³	n = 1578 17 (1%)	n = 1529 18 (1%)	n = 1529 18 (1%)

¹ The rates represent major bleeding on study medication up to 12 hours after dose.

² Aspirin therapy was administered concurrently (100 to 325 mg per day).

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

Major Bleeding Episodes in Deep Vein Thrombosis With or Without Pulmonary Embolism Treatment¹

Indication	Major Bleeding Episodes in Deep Vein Thrombosis With or Without Pulmonary Embolism Treatment ¹		
	Dosing Regimen		
	Lovenox Inj. 1.5 mg/kg q.d. SC	Lovenox Inj. 1 mg/kg q.12h SC	Heparin aPTT Adjusted i.v. Therapy
Treatment of DVT and PE	n = 298 9 (3%)	n = 559 9 (2%)	n = 554 9 (2%)

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

² All patients also received warfarin sodium (dose-adjusted according to PT) to achieve an INR of 2.0 to 3.0, commencing within 72 hours of Lovenox Injection or standard heparin therapy and continuing for up to 90 days.

Thrombocytopenia:

see WARNINGS: Thrombocytopenia.

Elevations of Serum Aminotransferases: Asymptomatic increases in aspartate (AST [SGOT]) and alanine (ALT [SGPT]) aminotransferase levels greater than three times the upper limit of normal of the laboratory reference range have been reported in up to 6.1% and 5.9% of patients, respectively, during treatment with Lovenox Injection. Similar significant increases in aminotransferase levels have also been observed in patients and healthy volunteers treated with heparin and other low molecular weight heparins. Such elevations are fully reversible and are rarely associated with increases in bilirubin.

Since aminotransferase determinations are important in the differential diagnosis of myocardial infarction, liver disease, and pulmonary emboli, elevations that might be caused by drugs like Lovenox Injection should be interpreted with caution.

Local Reactions:

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

Biofeedback Cuts BP in Type 2 Diabetes

BY MIRIAM E. TUCKER
Senior Writer

COPENHAGEN — Self-treatment with a biofeedback device that guides breathing can significantly lower blood pressure among patients with type 2 diabetes, Dr. Moshe H. Schein reported at the annual meeting of the European Association for the Study of Diabetes.

The device, called RESPerATE, is made by InterCure Ltd., Lod, Israel. It

was approved for use by the Food and Drug Administration in 2002 for use in stress reduction and as adjunctive treatment for hypertension, together with other pharmacologic and nonpharmacologic interventions. It works by using melodic tones to guide the patient through progressively slower inhalation and exhalation.

Previous data have shown that the device-guided technique results in significant blood pressure reductions among

hypertensive patients who use it at home on a daily basis (*J. Hum. Hypertens.* 2001;15:271-8).

In the new study, a total of 60 patients with type 2 diabetes who had blood pressures greater than 130/80 mm Hg were randomized to use of the device for 15 minutes a day along with usual treatment, or to usual treatment alone for 8 weeks. The group was 60% male, with a mean age of 64 years and a mean body mass index of 30 kg/m².

At baseline, mean blood pressure was 149/82 mm Hg in the treatment group and 146/81 mm Hg in the control group, even though the majority of patients—78% of the treatment group and 89% of the controls—were taking blood pressure medication, said Dr. Schein, director of the Family Medicine Unit, Hadassah University Hospital, Jerusalem.

Systolic blood pressure dropped by 9.5

Compared with normotensive men with a history of cardiovascular disease, those with prehypertension as defined by Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC) VII had an 18% greater risk of cardiovascular death after adjustment for age, smoking, alcohol intake, diabetes, physical activity, body mass index, and geographic region. Prehypertensive women had a 21% increase in risk.

Men and women with stage 1 hypertension had risk increases of 24% and 62%. Cardiovascular mortality was increased by 71% in men with stage 2 hypertension and by 72% in stage 2 women. ■

Other:

Other adverse effects that were thought to be possibly or probably related to treatment with Lovexin Injection, heparin, or placebo in clinical trials with patients undergoing hip or knee replacement surgery, abdominal or colorectal surgery, or treatment for DVT and that occurred at a rate of at least 2% in the Lovexin Injection group, are provided below.

Adverse Event	Dosing Regimen			
	Lovexin Inj. 40 mg q.d. SC n = 1229		Heparin 5000 U q8h SC n = 1234	
	Severe	Total	Severe	Total
Hemorrhage	<1%	7%	<1%	6%
Anemia	<1%	3%	<1%	3%
Ecchymosis	0%	3%	0%	3%

¹ Excluding unrelated adverse events.

Adverse Events Occurring at ≥2% Incidence in Lovexin Injection Treated Patients Undergoing Hip or Knee Replacement Surgery

Adverse Event	Dosing Regimen							
	Lovexin Inj. 40 mg q.d. SC n = 288 ²		Lovexin Inj. 30 mg q12h SC n = 1080		Heparin 15,000 U/24h SC n = 766		Placebo q12h SC n = 115	
	Severe	Total	Severe	Total	Severe	Total	Severe	Total
Fever	0%	8%	0%	0%	<1%	5%	<1%	4%
Hemorrhage	<1%	13%	0%	5%	<1%	4%	1%	4%
Nausea	0%	16%	0%	<2%	<1%	3%	<1%	2%
Anemia	0%	16%	0%	<2%	<1%	2%	2%	5%
Edema	0%	6%	0%	0%	<1%	2%	<1%	2%
Peripheral edema	0%	6%	0%	0%	<1%	3%	<1%	4%

¹ Excluding unrelated adverse events.

² Data represents Lovexin Injection 40 mg SC once a day initiated up to 12 hours prior to surgery in 288 hip replacement surgery patients who received Lovexin Injection peri-operatively in an unblinded fashion in one clinical trial.

³ Data represents Lovexin Injection 40 mg SC once a day given in a blinded fashion as extended prophylaxis at the end of the peri-operative period in 131 of the original 288 hip replacement surgery patients for up to 21 days in one clinical trial.

Adverse Events Occurring at ≥2% Incidence in Lovexin Injection Treated Medical Patients With Severely Restricted Mobility During Acute Illness

Adverse Event	Dosing Regimen	
	Lovexin Inj. 40 mg q.d. SC n = 360	Placebo q.d. SC n = 362
	%	%
Dyspnea	3.3	5.2
Thrombocytopenia	2.8	2.8
Confusion	2.2	1.1
Diarrhea	2.2	1.7
Nausea	2.5	1.7

¹ Excluding unrelated and unlikely adverse events.

Adverse Events in Lovexin Injection Treated Patients With Unstable Angina or Non-Q-Wave Myocardial Infarction:

Non-hemorrhagic clinical events reported to be related to Lovexin Injection therapy occurred at an incidence of ≤1%. Non-major hemorrhagic episodes, primarily injection site ecchymosis and hematomas, were more frequently reported in patients treated with SC Lovexin Injection than in patients treated with i.v. heparin. Serious adverse events with Lovexin Injection or heparin in a clinical trial in patients with unstable angina or non-Q-wave myocardial infarction that occurred at a rate of at least 0.5% in the Lovexin Injection group, are provided below (respectively of relationship to drug therapy).

Serious Adverse Events Occurring at ≥0.5% Incidence in Lovexin Injection Treated Patients With Unstable Angina or Non-Q-Wave Myocardial Infarction

Adverse Event	Dosing Regimen	
	Lovexin Inj. 1 mg/kg q12h SC n = 1578	Heparin aPTT Adjusted i.v. Therapy n = 1529
	n (%)	n (%)
Atrial fibrillation	11 (0.70)	3 (0.20)
Heart failure	15 (0.95)	11 (0.72)
Lung edema	11 (0.70)	11 (0.72)
Pneumonia	13 (0.82)	9 (0.59)

Adverse Events Occurring at ≥2% Incidence in Lovexin Injection Treated Patients Undergoing Treatment of Deep Vein Thrombosis With or Without Pulmonary Embolism

Adverse Event	Dosing Regimen			
	Lovexin Inj. 1.5 mg/kg q.d. SC n = 298		Heparin aPTT Adjusted i.v. Therapy n = 544	
	Severe	Total	Severe	Total
Hemorrhage	0%	5%	0%	3%
Injection Site Pain	0%	2%	0%	2%
Hematuria	0%	2%	0%	<1%

¹ Excluding unrelated adverse events.

Ongoing Safety Surveillance:

Since 1993, there have been over 80 reports of epidural or spinal hematoma formation with concurrent use of Lovexin Injection and spinal/epidural anesthesia or spinal puncture. The majority of patients had a post-operative indwelling epidural catheter placed for analgesia or received additional drugs affecting hemostasis such as NSAIDs. Many of the epidural or spinal hematomas caused neurologic injury, including long-term or permanent paralysis. Because these events were reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

Other Ongoing Safety Surveillance Reports:

Local reactions at the injection site (i.e., skin necrosis, nodules, inflammation, oozing), systemic allergic reactions (i.e., pruritus, urticaria, anaphylactoid reactions), vesiculobullous rash, rare cases of hypersensitivity cutaneous vasculitis, purpura, thrombocytosis, and thrombocytopenia with thrombosis (see WARNINGS, Thrombocytopenia). Very rare cases of hyperlipidemia have been reported, with one case of hyperlipidemia, with marked hypertriglyceridemia, reported in a diabetic pregnant woman; causality has not been determined.

OVERDOSAGE

Symptoms/Treatment:

Accidental overdosage following administration of Lovexin Injection may lead to hemorrhagic complications. Injected Lovexin Injection may be largely neutralized by the slow i.v. injection of protamine sulfate (1% solution). The dose of protamine sulfate should be equal to the dose of Lovexin Injection injected: 1 mg protamine sulfate should be administered to neutralize 1 mg Lovexin injection; if enoxaparin sodium was administered in the previous 8 hours. An infusion of 0.5 mg protamine per 1 mg

of enoxaparin sodium may be administered if enoxaparin sodium was administered greater than 8 hours previous to the protamine administration, or if it has been determined that a second dose of protamine is required. The second infusion of 0.5 mg protamine sulfate per 1 mg of Lovexin Injection may be administered if the aPTT measured 2 to 4 hours after the first infusion remains prolonged. After 12 hours of the enoxaparin sodium injection, protamine administration may not be required. However, even with higher doses of protamine, the aPTT may remain more prolonged than under normal conditions found following administration of 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 SC 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

All patients should be evaluated for a bleeding disorder before administration of Lovexin Injection, unless the medication is needed urgently. Since coagulation parameters are unsuitable for monitoring Lovexin Injection activity, routine monitoring of coagulation parameters is not required (see PRECAUTIONS, Laboratory Tests).

Note: Lovexin Injection is available in two concentrations:

- 1. 100 mg/mL Concentration:** 30 mg / 0.3 mL and 40 mg / 0.4 mL prefilled single-dose syringes, 60 mg / 0.6 mL, 80 mg / 0.8 mL, and 100 mg / 1 mL prefilled, graduated, single-dose syringes, 300 mg / 3.0 mL multiple-dose vials.
- 2. 150 mg/mL Concentration:** 120 mg / 0.8 mL and 150 mg / 1 mL prefilled, graduated, single-dose syringes.

Adult Dosage:

Abdominal Surgery: In patients undergoing abdominal surgery who are at risk for thromboembolic complications, the recommended dose of Lovexin Injection is **40 mg once a day** administered by SC injection with the initial dose given 2 hours prior to surgery. The usual duration of administration is 7 to 10 days; up to 12 days administration has been well tolerated in clinical trials.

Hip or Knee Replacement Surgery: In patients undergoing hip or knee replacement surgery, the recommended dose of Lovexin Injection is **30 mg every 12 hours** administered by SC injection. Provided that hemostasis has been established, the initial dose should be given 12 to 24 hours after surgery. For hip replacement surgery, a dose of **40 mg once a day SC**, given initially 12 (±3) hours prior to surgery, may be considered.

Following the initial phase of thromboprophylaxis in hip replacement surgery patients, continued prophylaxis with Lovexin Injection 40 mg once a day administered by SC injection for 3 weeks is recommended. The usual duration of administration is 7 to 10 days; up to 14 days administration has been well tolerated in clinical trials.

Medical Patients During Acute Illness: In medical patients at risk for thromboembolic complications due to severely restricted mobility during acute illness, the recommended dose of Lovexin Injection is **40 mg once a day** administered by SC injection. The usual duration of administration is 6 to 11 days; up to 14 days of Lovexin Injection has been well tolerated in the controlled clinical trial.

Unstable Angina and Non-Q-Wave Myocardial Infarction: In patients with unstable angina or non-Q-wave myocardial infarction, the recommended dose of Lovexin Injection is **1 mg/kg administered SC every 12 hours** in conjunction with oral aspirin therapy (100 to 325 mg once daily). Treatment with Lovexin Injection should be prescribed for a minimum of 2 days and continued until clinical stabilization. To minimize the risk of bleeding following vascular instrumentation during the treatment of unstable angina, adhere precisely to the intervals recommended between Lovexin Injection doses. The vascular access sheath for instrumentation should remain in place for 6 to 8 hours following a dose of Lovexin Injection. 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. The usual duration of treatment is 2 to 8 days; up to 12.5 days of Lovexin Injection has been well tolerated in clinical trials.

Treatment of Deep Vein Thrombosis With or Without Pulmonary Embolism: In **outpatient treatment**, patients with acute deep vein thrombosis without pulmonary embolism who can be treated at home, the recommended dose of Lovexin Injection is **1 mg/kg every 12 hours** administered SC. In **inpatient (hospital) treatment**, patients with acute deep vein thrombosis with pulmonary embolism or patients with acute deep vein thrombosis without pulmonary embolism (who are not candidates for outpatient treatment), the recommended dose of Lovexin Injection is **1 mg/kg every 12 hours** administered SC or **1.5 mg/kg once a day** administered SC at the same time every day. In both outpatient and inpatient (hospital) treatments, warfarin sodium therapy should be initiated when appropriate (usually within 72 hours of Lovexin Injection). Lovexin Injection should be continued for a minimum of 5 days and until a therapeutic oral anticoagulant effect has been achieved (International Normalization Ratio 2.0 to 3.0). The average duration of administration is 7 days; up to 17 days of Lovexin Injection administration has been well tolerated in controlled clinical trials.

Renal Impairment:

Although no dose adjustment is recommended in patients with moderate (creatinine clearance 30-50 mL/min) and mild (creatinine clearance 50-80 mL/min) renal impairment, all such patients should be observed carefully for signs and symptoms of bleeding. The recommended prophylaxis and treatment dosage regimens for patients with severe renal impairment (creatinine clearance <30 mL/min) are described in the following table (see CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations and PRECAUTIONS, Renal Impairment).

Indication	Dosage Regimen
Prophylaxis in abdominal surgery	30 mg administered SC once daily
Prophylaxis in hip or knee replacement surgery	30 mg administered SC once daily
Prophylaxis in medical patients during acute illness	30 mg administered SC once daily
Prophylaxis of ischemic complications of unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin	1 mg/kg administered SC once daily
Inpatient treatment of acute deep vein thrombosis with or without pulmonary embolism, when administered in conjunction with warfarin sodium	1 mg/kg administered SC once daily
Outpatient treatment of acute deep vein thrombosis without pulmonary embolism, when administered in conjunction with warfarin sodium	1 mg/kg administered SC once daily

Administration:

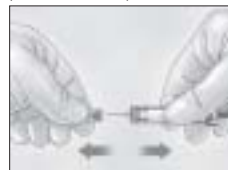
Lovexin Injection is a clear, colorless to pale yellow sterile solution, and as with other parenteral drug products, should be inspected visually for particulate matter and discoloration prior to administration. The use of a tuberculin syringe or equivalent is recommended when using Lovexin multiple-dose vials to assure withdrawal of the appropriate volume of drug. Lovexin Injection is administered by SC injection. It must not be administered by intramuscular injection. Lovexin Injection is intended for use under the guidance of a physician. Patients may self-inject only if their physician determines that it is appropriate and with medical follow-up, as necessary. Proper training in subcutaneous injection technique (with or without the assistance of an injection device) should be provided.

Subcutaneous Injection Technique: Patients should be lying down and Lovexin Injection administered by deep SC injection. To avoid the loss of drug when using the 30 and 40 mg prefilled syringes, do not expel the air bubble from the syringe before the injection. Administration should be alternated between the left and right antero-

LOVENOX® (enoxaparin sodium injection)

lateral 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. To minimize bruising, do not rub the injection site after completion of the injection. Lovexin Injection prefilled syringes and graduated prefilled syringes are available with a system that shields the needle after injection.

- Remove the needle shield by pulling it straight off the syringe. If adjusting the dose is required, the dose adjustment must be done prior to injecting the prescribed dose to the patient.



- Inject using standard technique, pushing the plunger to the bottom of the syringe.



- Remove the syringe from the injection site keeping your finger on the plunger rod.



- Orienting the needle away from you and others, activate the safety system by firmly pushing the plunger rod. The protective sleeve will automatically cover the needle and an audible "click" will be heard to confirm shield activation.



- Immediately dispose of the syringe in the nearest sharps container.



- NOTE:**
 - The safety system can only be activated once the syringe has been emptied.
 - Activation of the safety system must be done only after removing the needle from the patient's skin.
 - Do not replace the needle shield after injection.
 - The safety system should not be sterilized.
 - Activation of the safety system may cause minimal splatter of fluid. For optimal safety activate the system while orienting it downwards away from yourself and others.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Keep out of the reach of children.

¹ Lepercq J, Conard J, Borel-Delron A, et al. Venous thromboembolism during pregnancy: a retrospective study of enoxaparin safety in 624 pregnancies. *Br J Obstet Gynecol* 2001; 108 (11): 1134-40.

Sanofi-aventis U.S. LLC
Bridgewater, NJ 08807

Multiple-dose vials also manufactured by DSM Pharmaceuticals, Inc.
Greenville, NC 27835

Manufactured for:
sanofi-aventis U.S. LLC
Bridgewater, NJ 08807

© 2006 sanofi-aventis U.S. LLC.

Brief Summary of Prescribing Information Rev. September 2006

LOV-SEP06-B-Aa



INTERCURE LTD.

The RESPerATE device uses melodic tones to slow the patient's breathing.

mm Hg in the group using the device, compared with an increase of 2.1 mm Hg among the controls, a significant difference between the two groups.

The change in pulse pressure also was significantly different at 2 months; it dropped by 5.9 mm Hg from a mean of 67 mm Hg at baseline in the guided-breathing group, and increased by 3.6 mm Hg from a mean of 66 mm Hg in the controls.

Diastolic blood pressure dropped slightly in both groups, by 3.5 mm Hg in the guided-breathing patients and by 1.5 mm Hg among the controls. That difference was not significant.

There was a dose-response relationship between use of the device and systolic blood pressure reduction: The longer the patient spent in the slow breathing exercise, the greater the drop. (Although patients had been instructed to perform the device-guided breathing exercise daily, they actually did it for a mean of 5.6 sessions per week. However, the duration of each session lasted 15.9 minutes, slightly longer than the instructed 15 minutes, and patients spent a mean of 40.4 minutes per week in slow breathing.)

Blood pressure control—defined as 130/80 mm Hg or below—was achieved by 8 of 30 (27%) in the device group, compared with just 2 of the 30 (7%) of the controls, Dr. Schein reported. ■