

FDA Moving to Upgrade Device Safety Vigilance

BY ALICIA AULT

Associate Editor, Practice Trends

The Food and Drug Administration announced on Nov. 9 that it is taking steps to improve its postmarketing surveillance of medical device safety, including moving ahead on a proposal to require electronic reporting of adverse events.

The agency said it has created an action plan based on a major review that was

completed in 2005. That review looked at how the Center for Radiological Devices and Health (CDRH) handles recalls and enforcement actions against manufacturers that are not in compliance with FDA rules.

"Today's report details a number of action items that we believe will transform the postmarketing safety program," said Dr. Daniel Schultz, director of CDRH, in a briefing with reporters.

The FDA will focus on making improvements in four major areas: collabora-

tion among experts within CDRH, data systems, communications with patients and physicians about risks and benefits, and enforcement.

CDRH leaders will encourage more cross-organizational collaboration so that premarket, postmarket, and enforcement efforts are better coordinated, Dr. Schultz said.

Some of the biggest changes will come in data collection and analysis. The agency hopes to integrate its passive adverse

events reporting system (Manufacturer and User Facility Device Experience Database, also known as MAUDE) and its active system, the Medical Product Safety Device Network (MedSun), Dr. Schultz said. Currently, 350 hospitals have been trained to report device problems on MedSun. One goal is to recruit more facilities and find a way to upgrade reporting so it is closer to real time.

The agency also hopes to require manufacturers and others to electronically report



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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 (10 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 preterm 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 sulfonpyrazone. 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 who 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.¹

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 | Dosing Regimen | |
|--------------------|-------------------------------|--------------------------|
| | Lovenox Inj. 40 mg q.d. SC | Heparin 5000 U q8h SC |
| Abdominal Surgery | n = 555 23 (4%) | n = 560 16 (3%) |
| Colorectal Surgery | n = 673 28 (4%) | 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, intracranial, and intracranial hemorrhages were always considered major.

Major Bleeding Episodes Following Hip or Knee Replacement Surgery¹

| Indications | Dosing Regimen | |
|--|---|----------------------------|
| | Lovenox Inj. 40 mg q.d. SC | Heparin 15,000 U/24h SC |
| Hip Replacement Surgery Without Extended Prophylaxis ² | n = 786 31 (4%) | n = 541 32 (6%) |
| Hip Replacement Surgery With Extended Prophylaxis | Peri-operative Period ³ n = 288 4 (2%) Extended n = 221 0 (0%) Prophylaxis Period ⁴ | |
| Knee Replacement Surgery Without Extended Prophylaxis ² | n = 294 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, intracranial 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 | Dosing Regimen | | |
|---------------------------------------|--|--|----------------------|
| | Lovenox Inj. ² 20 mg q.d. SC | Lovenox Inj. ² 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 | Dosing Regimen | |
|--|--|---|
| | Lovenox Inj. ¹ 1 mg/kg q12h SC | Heparin ¹ aPTT Adjusted i.v. Therapy |
| Unstable Angina and Non-Q-Wave MI ^{2,3} | n = 1578 17 (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. Intracranial, retroperitoneal, and intracranial hemorrhages were always considered major.

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

| Indication | Dosing Regimen ² | | |
|-------------------------|-----------------------------------|---------------------------------|--|
| | Lovenox Inj. 1.5 mg/kg q.d. SC | Lovenox Inj. 1 mg/kg q12h SC | Heparin aPTT Adjusted i.v. Therapy |
| Treatment of DVT and PE | n = 298 5 (2%) | 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, intracranial, 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.

adverse events. Currently, the FDA receives about 200,000 reports to MAUDE each year, and the majority are on paper, which delays entry into the system and analysis for any kind of safety signal, said Dr. Schultz. The FDA has been piloting an electronic reporting program, and is in the process of writing a rule to require electronic reporting, he said.

Once data are being reported and analyzed more quickly, enforcement will be more timely also, he said. It will also let the FDA focus enforcement efforts on the highest-risk products, Dr. Schultz said. "When enforcement is necessary, it needs to be done quickly, accurately, and

in a way that's meaningful and corrects problems," he said.

The FDA also aims to improve its communications to health professionals and consumers—whether the communications are notices about unsafe devices or simply background on safety and efficacy of products. CDRH will redesign its Web site to be more consumer-friendly. It will also take a closer look at how best to give out data—and when—on a potentially faulty device.

CDRH is hoping to accomplish most of its planned "action points" without seeking additional funding, at least in the near term, Dr. Schultz said. ■

Other: Other adverse effects that were thought to be possibly or probably related to treatment with Lovenox 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 Lovenox Injection group, are provided below.

Adverse Events Occurring at ≥2% Incidence in Lovenox Injection Treated Patients Undergoing Abdominal or Colorectal Surgery

| Adverse Event | Dosing Regimen | | | |
|---------------|-------------------------------------|-------|--------------------------------|-------|
| | Lovenox Inj. 40 mg q.d. SC n = 1228 | | 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% |

† Excluding unrelated adverse events.

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

| Adverse Event | Dosing Regimen | | | | | | | | | |
|------------------|----------------------------|-------|----------------------------|-------|-------------------------|-------|-----------------|-------|--------|-------|
| | Lovenox Inj. 40 mg q.d. SC | | Lovenox Inj. 30 mg q12h SC | | Heparin 15,000 U/24h SC | | Placebo q12h SC | | | |
| | Severe | Total | Severe | Total | Severe | Total | Severe | Total | Severe | Total |
| Fever | 0% | 8% | 0% | 0% | <1% | 5% | <1% | 4% | 0% | 3% |
| Hemorrhage | <1% | 13% | 0% | 5% | <1% | 4% | 1% | 4% | 0% | 3% |
| Nausea | 0% | 16% | 0% | <2% | <1% | 3% | <1% | 2% | 0% | 2% |
| Anemia | 0% | 16% | 0% | <2% | <1% | 2% | 2% | 5% | <1% | 7% |
| Edema | 0% | 6% | 0% | 0% | <1% | 2% | <1% | 2% | 0% | 2% |
| Peripheral edema | 0% | 6% | 0% | 0% | <1% | 3% | <1% | 4% | 0% | 3% |

† Excluding unrelated adverse events.
 2 Data represents Lovenox Injection 40 mg SC once a day initiated up to 12 hours prior to surgery in 288 hip replacement surgery patients who received Lovenox Injection peri-operatively in an unblinded fashion in one clinical trial.
 3 Data represents Lovenox 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 Lovenox Injection Treated Patients With Severely Restricted Mobility During Acute Illness

| Adverse Event | Lovenox Inj. 40 mg q.d. SC n = 360 | | Placebo q.d. SC n = 362 | |
|------------------|------------------------------------|-------|-------------------------|-------|
| | Severe | Total | Severe | Total |
| Dyspnea | 0% | 3.3 | 0% | 5.2 |
| Thrombocytopenia | <1% | 2.8 | <1% | 2.8 |
| Confusion | 0% | 2.2 | 0% | 1.1 |
| Diarrhea | 0% | 2.2 | 0% | 1.7 |
| Nausea | 0% | 2.5 | 0% | 1.7 |

† Excluding unrelated and unlikely adverse events.

Adverse Events in Lovenox Injection Treated Patients With Unstable Angina or Non-Q-Wave Myocardial Infarction: Non-hemorrhagic clinical events reported to be related to Lovenox Injection therapy occurred at an incidence of ≤1%. Non-major hemorrhagic episodes, primarily injection site ecchymoses and hematomas, were more frequently reported in patients treated with SC Lovenox Injection than in patients treated with i.v. heparin. Serious adverse events with Lovenox 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 Lovenox Injection group, are provided below (respective of relationship to drug therapy).

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

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

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

| Adverse Event | Dosing Regimen | | | | | |
|---------------------------|--|-------|--------------------------------------|-------|--|-------|
| | Lovenox Inj. 1.5 mg/kg q.d. SC n = 298 | | Lovenox Inj. 1 mg/kg q12h SC n = 559 | | Heparin aPTT Adjusted i.v. Therapy n = 544 | |
| | Severe | Total | Severe | Total | Severe | Total |
| Injection Site Hemorrhage | 0% | 5% | 0% | 3% | <1% | <1% |
| Injection Site Pain | 0% | 2% | 0% | 2% | 0% | 0% |
| Hematoma | 0% | 2% | 0% | <1% | <1% | 2% |

† 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 Lovenox 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, thrombocytopenia, 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 Lovenox Injection may lead to hemorrhagic complications. Injected Lovenox 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 Lovenox Injection injected: 1 mg protamine sulfate should be administered to neutralize 1 mg Lovenox 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 Lovenox 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 anaphylactoid 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.

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

Note: Lovenox 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 Lovenox 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 Lovenox Injection is **30 mg every 12 hours** administered by SC injection. Provided that hemostasis has been established, the initial dose should be given **12 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 Lovenox 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 Lovenox 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 Lovenox 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 Lovenox Injection is **1 mg/kg administered SC every 12 hours** in conjunction with oral aspirin therapy (100 to 325 mg once daily). Treatment with Lovenox 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 Lovenox Injection doses. The vascular access sheath for instrumentation should remain in place for 6 to 8 hours following a dose of Lovenox 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 Lovenox 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 Lovenox 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 Lovenox 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 Lovenox Injection). Lovenox 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 Lovenox 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 | Dosing Regimen (creatinine clearance <30 mL/minute) | |
|---|---|------------------------------------|
| | Lovenox Inj. | Heparin |
| Prophylaxis in abdominal surgery | 30 mg administered SC once daily | aPTT Adjusted i.v. Therapy n = 544 |
| 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: Lovenox 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 Lovenox multiple-dose vials to assure withdrawal of the appropriate volume of drug. Lovenox Injection is administered by SC injection. It must not be administered by intramuscular injection. Lovenox 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 Lovenox 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-

Emergency Trial Rule Under Scrutiny by FDA

BY ELIZABETH MEHCATIE
 Senior Writer

ROCKVILLE, MD. — The Food and Drug Administration is reviewing a decade-old regulation that allows clinical studies of emergency treatments, including automated defibrillator implantation, to be conducted without obtaining in-

formed consent in people with certain life-threatening conditions.

The FDA's reappraisal and proposed revision of the rule were prompted by concerns that current safeguards do not provide enough protection of human subjects, and by comments that the safeguards are too onerous and impede important research.

At present, a narrow exception to the informed consent requirement exists in the case of patients who cannot provide consent because of their conditions and who have no family members available to give consent.

To be exempt from informed consent, an investigation must meet certain criteria, including the following:

- The patient is in a life-threatening situation.
- The available treatments are unproven or not satisfactory.
- Evidence supports the prospect of direct benefit to the individual.

Since the regulation went into effect in October 1996, the FDA has received 56 requests to conduct emergency research under this rule. A total of 21 studies have been conducted, are being conducted, or are about to start enrollment, according to the FDA.

The FDA has issued draft guidance geared toward institutional review boards, clinical investigators, and sponsors developing and conducting emergency research. It also sponsored a public hearing in October on emergency research.

At that hearing, presenters offered examples of emergency research that could not otherwise have been done without the exception.

Although the current rules could be simplified, the exception to informed consent is critical, said Dr. Paul Pepe, professor of surgery, medicine, and public health, and Riggs Family Chair in emergency medicine at the University of Texas Southwestern Medical Center at Dallas.

"Studies of the automated external defibrillator are an example of the tremendous lifesaving potential of emergency treatments," he said. Such studies can also show that treatments that have been widely accepted and appear to be logical may in fact be harmful in some populations, he added. For example, intravenous fluid resuscitation was found to be harmful in certain trauma populations. If these studies had not been done, Dr. Pepe explained, many people would have died.

"Any revisions to current regulations should serve to expand the ability to perform the highest quality emergency research and to enhance patient protections through fairness, openness, and the use of all media that provide explicit detail regarding the research," Dr. Edward P. Sloan and Dr. Charles Cairns said in a statement on behalf of the American College of Emergency Physicians.

The FDA will review written comments on the guidance, as well as comments made at the hearing, to determine whether the rule should be modified. ■

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.

Lovenox 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-Derlon 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.

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 Greenville, NC 27835

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