

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020287/S010

FINAL PRINTED LABELING

FRAGMIN®
dalteparin sodium injection

For Subcutaneous Use Only

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 neurological 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 (also see WARNINGS, Hemorrhage and PRECAUTIONS, Drug Interactions).

DESCRIPTION

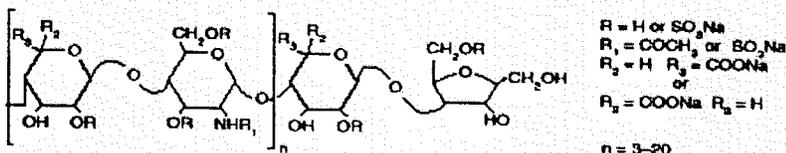
FRAGMIN Injection (dalteparin sodium injection) is a sterile, low molecular weight heparin. It is available in single-dose, prefilled syringes and a multiple-dose vial. With reference to the W.H.O. First International Low Molecular Weight Heparin Reference Standard, each syringe contains 2500 (16 mg dalteparin sodium) or 5000 (32 mg dalteparin sodium) anti-Factor Xa international units (IU) in 0.2 mL. Each 9.5 mL vial contains 10,000 (64 mg dalteparin sodium) anti-Factor Xa IU per 1 mL, for a total of 95,000 anti-Factor Xa IU per vial.

Each prefilled syringe also contains Water for Injection and sodium chloride, when required, to maintain physiologic ionic strength. The prefilled syringes are preservative free. Each multiple-dose vial also contains Water for Injection and 14 mg of benzyl alcohol per mL as a preservative. The pH of both formulations is 5.0 to 7.5.

Dalteparin sodium is produced through controlled nitrous acid depolymerization of sodium heparin from porcine intestinal mucosa followed by a chromatographic purification process. It is composed of strongly acidic sulphated polysaccharide chains (oligosaccharide, containing 2,5-anhydro-D-mannitol residues as end groups) with an average molecular weight of 5000 and about 90% of the material within the range 2000-9000. The molecular weight distribution is:

< 3000 daltons	3.0-15.0%
3000 to 8000 daltons	65.0-78.0%
> 8000 daltons	14.0-26.0%

Structural formula



CLINICAL PHARMACOLOGY

Dalteparin is a low molecular weight heparin with antithrombotic properties. It acts by enhancing the inhibition of Factor Xa and thrombin by antithrombin. In man, dalteparin potentiates preferentially the inhibition of coagulation Factor Xa, while only slightly affecting clotting time, e.g., activated partial thromboplastin time (APTT).

Pharmacodynamics:

Doses of FRAGMIN Injection of up to 10,000 anti-Factor Xa IU administered subcutaneously as a single dose or two 5000 IU doses 12 hours apart to healthy subjects do not produce a significant change in platelet aggregation, fibrinolysis, or global clotting tests such as prothrombin time (PT), thrombin time (TT) or APTT. Subcutaneous (s.c.) administration of doses of 5000 IU bid of FRAGMIN for seven consecutive days to patients undergoing abdominal surgery did not markedly affect APTT, Platelet Factor 4 (PF4), or lipoprotein lipase.

Pharmacokinetics:

Mean peak levels of plasma anti-Factor Xa activity following single s.c. doses of 2500, 5000 and 10,000 IU were 0.19 ± 0.04 , 0.41 ± 0.07 and 0.82 ± 0.10 IU/mL, respectively, and were attained in about 4 hours in most subjects. Absolute bioavailability in healthy volunteers, measured as the anti-Factor Xa activity, was $87 \pm 6\%$. Increasing the dose from 2500 to 10,000 IU resulted in an overall increase in anti-Factor Xa AUC that was greater than proportional by about one-third.

Peak anti-Factor Xa activity increased more or less linearly with dose over the same dose range. There appeared to be no appreciable accumulation of anti-Factor Xa activity with twice-daily dosing of 100 IU/kg s.c. for up to 7 days.

The volume of distribution for dalteparin anti-Factor Xa activity was 40 to 60 mL/kg. The mean plasma clearances of dalteparin anti-Factor Xa activity in normal volunteers following single intravenous bolus doses of 30 and 120 anti-Factor Xa IU/kg were 24.6 ± 5.4 and 15.6 ± 2.4 mL/hr/kg, respectively. The corresponding mean disposition half-lives are 1.47 ± 0.3 and 2.5 ± 0.3 hours.

Following intravenous doses of 40 and 60 IU/kg, mean terminal half-lives were 2.1 ± 0.3 and 2.3 ± 0.4 hours, respectively. Longer apparent terminal half-lives (3 to 5 hours) are observed following s.c. dosing, possibly due to delayed absorption. In patients with chronic renal insufficiency requiring hemodialysis, the mean terminal half-life of anti-Factor Xa activity following a single intravenous dose of 5000 IU FRAGMIN was 5.7 ± 2.0 hours, i.e. considerably longer than values observed in healthy volunteers, therefore, greater accumulation can be expected in these patients.

CLINICAL TRIALS

Unstable Angina and Non-Q-wave Myocardial Infarction:

In a double-blind randomized placebo-controlled clinical trial, 1506 patients who recently experienced unstable angina with EKG changes or non-Q-wave myocardial infarction were randomized to FRAGMIN Injection 120 IU/kg every 12 hours subcutaneously (s.c.) or placebo every 12 hrs. s.c. In this trial, unstable angina was defined to include only angina with EKG changes. All patients, except when contraindicated, were treated concurrently with aspirin (75 mg per day) and beta blockers. Treatment was initiated within 72 hours of the event (the majority of patients received treatment within 24 hours) and continued for 5-8 days. The combined incidence of the double endpoint of death or myocardial infarction (MI) was lower for Fragmin Injection compared with placebo at 6 days after initiation of therapy. These results were observed in an analysis of all-randomized and all-treated patients. The combined incidence of death, MI, need for intravenous (i.v.) heparin or i.v. nitroglycerin, and revascularization was also lower for FRAGMIN than for placebo (see Table 1).

Table 1
Efficacy of FRAGMIN in Unstable Angina and Non-Q-wave Myocardial Infarction

Indication	Dosing Regimen	
	FRAGMIN 120 IU/kg/12 hr s.c.	Placebo q 12 hr s.c.
All Treated Unstable Angina and Non-Q-Wave MI Patients	746	760
Primary Endpoints- 6 day timepoint Death, MI	13/741 (1.8%) ¹	36/757 (4.8%)
Secondary Endpoints- 6 day timepoint		
Death, MI, i.v. heparin, i.v. nitroglycerin, Revascularization	59/739 (8.0%) ¹	106/756 (14.0%)

¹ p-value = 0.001

In a second randomized, controlled trial of 1482 patients designed to evaluate long-term treatment with FRAGMIN (days 6 to 45), data were also collected comparing 1-week (5 to 8 days) treatment of FRAGMIN 120 IU/kg every 12 hours s.c. with heparin at an APTT-adjusted dosage. All patients, except when contraindicated, were treated concurrently with aspirin (100 to 165 mg per day). The incidence of the combined triple endpoint of death, myocardial infarction, or recurrent angina during this 1-week treatment period (5 to 8 days) was 9.3% for Fragmin and 7.6% for heparin (p=0.323).

Hip Replacement Surgery:

In an open-label randomized study, FRAGMIN 5000 IU administered once daily s.c. was compared to warfarin sodium, administered orally, in patients undergoing hip replacement surgery. Treatment with FRAGMIN was initiated with a 2500 IU dose s.c. within 2 hours before surgery, followed by a 2500 IU s.c. dose the evening of the day of surgery. Then, a dosing regimen of FRAGMIN 5000 IU s.c. once daily was initiated on the first postoperative day. The first dose of warfarin sodium was given the evening before surgery, then continued daily at a dose adjusted for INR 2.0 to 3.0. Treatment in both groups was then continued for 5 to 9 days postoperatively. The incidence of total DVT, as determined by evaluable venography, was significantly lower for the group treated with FRAGMIN compared to patients treated with warfarin sodium (28/192 vs 49/190; p=0.006) [see Table 2].

Table 2
Efficacy of FRAGMIN in Hip Replacement Surgery

Indication	Dosing Regimen	
	<u>FRAGMIN</u> 5000 IU qd ¹ s.c.	<u>Warfarin Sodium</u> Qd ² oral
All Treated Hip Replacement Surgery Patients	271	279
Treatment Failures in Evaluable Patients		
DVT, Total	28/192 (14.6%) ³	49/190 (25.8%)
Proximal DVT	10/192 (5.2%) ⁴	16/190 (8.4%)
PE	2/271 (0.7%)	2/279 (0.7%)

- 1 The daily dose on the day of surgery was divided: 2500 IU was given two hours before surgery and again in the evening of the day of surgery.
- 2 Warfarin sodium dosage was adjusted to maintain a prothrombin time index of 1.4 to 1.5, corresponding to an International Normalized Ratio (INR) of approximately 2.5.
- 3 p-value = 0.006
- 4 p-value = 0.185

In a second study (single-center, double-blind) of 136 patients undergoing hip replacement surgery, FRAGMIN 5000 IU once daily s.c. starting the evening before surgery, was compared to heparin 5000 U s.c. tid, starting the morning of surgery. Treatment in both groups was continued for up to 9 days postoperatively. In the intent-to-treat analysis, the incidence of proximal DVT was significantly lower for patients treated with FRAGMIN compared to patients treated with heparin (6/67 vs 18/69; p=0.012). Further, the incidence of pulmonary embolism detected by lung scan was also significantly lower in the group treated with FRAGMIN (9/67 vs 19/69; p=0.032).

Abdominal Surgery:

FRAGMIN administered once daily s.c. beginning prior to surgery and continuing for 5 to 10 days after surgery, has been shown to prevent deep vein thrombosis (DVT) in patients at risk for thromboembolic complications. Data from two double-blind randomized controlled clinical trials performed in patients undergoing major abdominal surgery, summarized in the following tables, show that FRAGMIN 2500 IU was superior to placebo and similar to heparin in preventing DVT (see Tables 3 and 4).

Table 3
Efficacy of FRAGMIN in Abdominal Surgery

Indication	Dosing Regimen	
	<u>FRAGMIN</u> 2500 IU qd s.c.	<u>Placebo</u> Qd s.c.
All Treated Abdominal Surgery Patients	102	102
Treatment Failures in Evaluable Patients		
Total Thromboembolic Events	4/91 (4.4%) ¹	16/91 (17.6%)
Proximal DVT	0	5/91 (5.5%)
Distal DVT	4/91 (4.4%)	11/91 (12.1%)
PE	0	2/91 (2.2%) ²

1 p-value = 0.008

2 Both patients also had DVT, 1 proximal and 1 distal

Table 4
Efficacy of FRAGMIN in Abdominal Surgery

Indication	Dosing Regimen	
	<u>FRAGMIN</u> 2500 IU qd s.c.	<u>Heparin</u> 5000 U bid s.c.
All Treated Abdominal Surgery Patients	195	196
Treatment Failures in Evaluable Patients		
Total Thromboembolic Events	7/178 (3.9%) ¹	7/174 (4.0%)
Proximal DVT	3/178 (1.7%)	4/174 (2.3%)
Distal DVT	3/178 (1.7%)	3/174 (1.7%)
PE	1/178 (0.6%)	0

1 p-value = 0.74

Data from a double-blind randomized controlled trial show that FRAGMIN 5000 IU once daily is more effective than FRAGMIN 2500 IU once daily in preventing DVT in patients undergoing abdominal surgery with malignancy (see Table 5).

Table 5
Efficacy of FRAGMIN in Abdominal Surgery Patients with Malignancy

Indication	Dosing Regimen	
	FRAGMIN 2500 IU qd s.c.	FRAGMIN 5000 IU qd s.c.
All Treated Abdominal Surgery Patients	696	679
Treatment Failures in Evaluable Patients		
Total Thromboembolic Events		
Proximal DVT	99/656 (15.1%) ¹	60/645 (9.3%)
Distal DVT	18/657 (2.7%)	14/646 (2.2%)
PE		
Fatal	80/657 (12.2%)	41/646 (6.3%)
Non-fatal	1/674 (0.1%)	1/669 (0.1%)
	2	4

¹ p-value = 0.001

INDICATIONS AND USAGE

FRAGMIN Injection is indicated for the treatment of unstable angina and non-Q-wave myocardial infarction for the prevention of ischemic complications in patients on concurrent aspirin therapy (as described in CLINICAL TRIALS, Unstable Angina and Non-Q-Wave Myocardial Infarction).

FRAGMIN is also indicated for prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism:

- In patients undergoing hip replacement surgery;
- In patients undergoing abdominal surgery who are at risk for thromboembolic complications. Patients at risk include those who are over 40 years of age, obese, undergoing surgery under general anesthesia lasting longer than 30 minutes, or who have additional risk factors such as malignancy, or a history of deep venous thrombosis or pulmonary embolism.

CONTRAINDICATIONS

FRAGMIN Injection is contraindicated in patients with known hypersensitivity to the drug, active major bleeding, or thrombocytopenia associated with positive *in vitro* tests for anti-platelet antibody in the presence of FRAGMIN.

Patients undergoing regional anesthesia should not receive FRAGMIN for unstable angina or non-Q-wave myocardial infarction due to an increased risk of bleeding associated with the dosage of FRAGMIN recommended for unstable angina and non-Q-wave myocardial infarction.

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

WARNINGS

FRAGMIN Injection is not intended for intramuscular administration.

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

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

Hemorrhage:

FRAGMIN, like other anticoagulants, should be used with extreme caution in patients who have an increased risk of hemorrhage, such as those with severe uncontrolled hypertension, bacterial endocarditis, congenital or acquired bleeding disorders, active ulceration and angiodysplastic gastrointestinal disease, hemorrhagic stroke, or shortly after brain, spinal or ophthalmological surgery.

Spinal or epidural hematomas can occur with the associated use of low molecular weight heparins or heparinoids and neuraxial (spinal/epidural) anesthesia or spinal puncture, which can result in long-term or permanent paralysis. The risk of these events is higher with the use of indwelling epidural catheters or concomitant use of additional drugs affecting hemostasis such as NSAIDs (see boxed WARNING and ADVERSE REACTIONS, Ongoing Safety Surveillance).

As with other anticoagulants, bleeding can occur at any site during therapy with FRAGMIN. An unexpected drop in hematocrit or blood pressure should lead to a search for a bleeding site.

Thrombocytopenia:

In clinical trials, thrombocytopenia with platelet counts of $< 100,000/\text{mm}^3$ and $< 50,000/\text{mm}^3$ occurred in $< 1\%$ and $< 1\%$, respectively. In clinical practice, rare cases of thrombocytopenia with thrombosis have also been observed.

Thrombocytopenia of any degree should be monitored closely. Heparin-induced thrombocytopenia can occur with the administration of FRAGMIN. The incidence of this complication is unknown at present.

Miscellaneous:

The multiple-dose vial of FRAGMIN contains benzyl alcohol as a preservative. Benzyl alcohol has been reported to be associated with a fatal "Gasping Syndrome" in premature infants.

Because benzyl alcohol may cross the placenta, FRAGMIN preserved with benzyl alcohol should not be used in pregnant women (see PRECAUTIONS, Pregnancy Category B., Nonteratogenic Effects).

PRECAUTIONS

General:

FRAGMIN Injection should not be mixed with other injections or infusions unless specific compatibility data are available that support such mixing.

FRAGMIN should be used with caution in patients with bleeding diathesis, thrombocytopenia or platelet defects; severe liver or kidney insufficiency, hypertensive or diabetic retinopathy, and recent gastrointestinal bleeding.

If a thromboembolic event should occur despite dalteparin prophylaxis, FRAGMIN should be discontinued and appropriate therapy initiated.

Drug Interactions:

FRAGMIN should be used with care in patients receiving oral anticoagulants, platelet inhibitors, and thrombolytic agents because of increased risk of bleeding (see PRECAUTIONS, Laboratory Tests). Aspirin, unless contraindicated, is recommended in patients treated for unstable angina or non-Q-wave myocardial infarction (see DOSAGE AND ADMINISTRATION).

Laboratory Tests:

Periodic routine complete blood counts, including platelet count, and stool occult blood tests are recommended during the course of treatment with FRAGMIN. No special monitoring of blood clotting times (e.g., APTT) is needed.

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 FRAGMIN activity and, therefore, unsuitable for monitoring.

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 1.7 and 4.3%, respectively, of patients during treatment with FRAGMIN. Similar significant increases in transaminase levels have also been observed in patients 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 FRAGMIN should be interpreted with caution.

Carcinogenicity, Mutagenesis, Impairment of Fertility:

Dalteparin sodium has not been tested for its carcinogenic potential in long-term animal studies. It was not mutagenic in the *in vitro* Ames Test, mouse lymphoma cell forward mutation test and human lymphocyte chromosomal aberration test and in the *in vivo* mouse micronucleus test. Dalteparin sodium at subcutaneous doses up to 1200 IU/kg (7080 IU/m²) did not affect the fertility or reproductive performance of male and female rats.

Pregnancy: Pregnancy Category B.

Teratogenic Effects:

Reproduction studies with dalteparin sodium at intravenous doses up to 2400 IU/kg (14,160 IU/m²) in pregnant rats and 4800 IU/kg (40,800 IU/m²) in pregnant rabbits did not produce any evidence of impaired fertility or harm to the fetuses. 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.

Nonteratogenic Effects:

Cases of "Gasping Syndrome" have occurred when large amounts of benzyl alcohol have been administered (99 - 404 mg/kg/day). The 9.5 mL multiple-dose vial of FRAGMIN contains 14 mg/mL of benzyl alcohol.

Nursing Mothers:

It is not known whether dalteparin sodium is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when FRAGMIN is administered to a nursing mother.

Pediatric Use:

Safety and effectiveness in pediatric patients have not been established.

ADVERSE REACTIONS

Hemorrhage:

The incidence of hemorrhagic complications during treatment with FRAGMIN Injection has been low. The most commonly reported side effect is hematoma at the injection site. The incidence of bleeding may increase with higher doses; however, in abdominal surgery patients with malignancy, no significant increase in bleeding was observed when comparing FRAGMIN 5000 IU to either FRAGMIN 2500 IU or low dose heparin.

In a trial comparing FRAGMIN 5000 IU once daily to FRAGMIN 2500 IU once daily in patients undergoing surgery for malignancy, the incidence of bleeding events was 4.6% and 3.6%, respectively (n.s.). In a trial comparing FRAGMIN 5000 IU once daily to heparin 5000 U twice daily, the incidence of bleeding events was 3.2% and 2.7%, respectively (n.s.) in the malignancy subgroup.

Unstable Angina and Non-Q-wave Myocardial Infarction:

Table 6 summarizes major bleeding events that occurred with FRAGMIN, heparin, and placebo in clinical trials of unstable angina and non-Q-wave myocardial infarction.

Table 6
Major Bleeding Events in Unstable Angina and Non-Q-wave Myocardial Infarction

Indication	Dosing Regimen		
	<u>FRAGMIN</u> 120 IU/kg/12 hr s.c. ¹	<u>Heparin</u> i.v. and s.c. ²	<u>Placebo</u> q 12 hr s.c.
Unstable angina and non-Q-wave MI			
Major Bleeding Events ^{3, 4}	15/1497 (1.0%)	7/731 (1.0%)	4/760 (0.5%)

¹ Treatment was administered for 5 to 8 days.

² Heparin i.v. infusion for at least 48 hours, APPT 1.5 to 2 times control, then 12,500 U s.c. every 12 hours for 5 to 8 days.

³ Aspirin (75 to 165 mg per day) and beta blocker therapies were administered concurrently.

⁴ Bleeding events were considered major if (1) accompanied by a decrease in hemoglobin of ≥ 2 g/dL in connection with clinical symptoms; (2) a transfusion was required; (3) bleeding led to interruption of treatment or death; or (4) intracranial bleeding

Hip Replacement Surgery:

Table 7 summarizes: 1) all major bleeding events and, 2) other bleeding events possibly or probably related to treatment with FRAGMIN, warfarin, or heparin in clinical trials of hip replacement surgery.

Table 7
Bleeding Events in Hip Replacement Surgery

Indication	FRAGMIN vs Warfarin Sodium		FRAGMIN vs Heparin	
	Dosing Regimen		Dosing Regimen	
Hip Replacement Surgery	FRAGMIN 5000 IU qd s.c. (n = 274 ²)	Warfarin Sodium ¹ oral (n = 279)	FRAGMIN 5000 IU qd s.c. (n = 69 ⁴)	Heparin 5000 U tid s.c. (n = 69)
Major Bleeding Events ³	7/274 (2.6%)	1/279 (0.4%)	0	3/69 (4.3%)
Other Bleeding Events ⁵				
Hematuria	8/274 (2.9%)	5/279 (1.8%)	0	0
Wound Hematoma	6/274 (2.2%)	0	0	0
Injection Site Hematoma	3/274 (1.1%)	NA	2/69 (2.9%)	7/69 (10.1%)

- 1 Warfarin sodium dosage was adjusted to maintain a prothrombin time index of 1.4 to 1.5, corresponding to an International Normalized Ratio (INR) of approximately 2.5.
- 2 Includes three treated patients who did not undergo a surgical procedure.
- 3 A bleeding event was considered major if: 1) hemorrhage caused a significant clinical event, 2) it was associated with a hemoglobin decrease of ≥ 2 g/dL or transfusion of 2 or more units of blood products, 3) it resulted in reoperation due to bleeding, or 4) it involved retroperitoneal or intracranial hemorrhage.
- 4 Includes two treated patients who did not undergo a surgical procedure.
- 5 Occurred at a rate of at least 2% in the group treated with FRAGMIN 5000 IU once daily.

Six of the patients treated with FRAGMIN experienced seven major bleeding events. Two of the events were wound hematoma (one requiring reoperation), three were bleeding from the operative site, one was intraoperative bleeding due to vessel damage, and one was gastrointestinal bleeding. None of the patients experienced retroperitoneal or intracranial hemorrhage nor died of bleeding complications.

Abdominal Surgery:

Table 8 summarizes bleeding events that occurred in clinical trials which studied FRAGMIN 2500 and 5000 IU administered once daily to abdominal surgery patients.

Table 8
Bleeding Events in Abdominal Surgery

Indication	FRAGMIN vs Heparin				FRAGMIN vs Placebo		FRAGMIN vs FRAGMIN	
	Dosing Regimen				Dosing Regimen		Dosing Regimen	
	FRAGMIN 2500 IU qd s.c.	Heparin 5000 U bid s.c.	FRAGMIN 5000 IU qd s.c.	Heparin 5000 U bid s.c.	FRAGMIN 2500 IU qd s.c.	Placebo qd s.c.	FRAGMIN 2500 IU qd s.c.	FRAGMIN 5000 IU qd s.c.
Abdominal Surgery								
Postoperative Transfusions	26/459 (5.7%)	36/454 (7.9%)	81/508 (15.9%)	63/498 (12.7%)	14/182 (7.7%)	13/182 (7.1%)	89/1025 (8.7%)	125/1033 (12.1%)
Wound Hematoma	16/467 (3.4%)	18/467 (3.9%)	12/508 (2.4%)	6/498 (1.2%)	2/79 (2.5%)	2/77 (2.6%)	1/1030 (0.1%)	4/1039 (0.4%)
Reoperation due to Bleeding	2/392 (0.5%)	3/392 (0.8%)	4/508 (0.8%)	2/498 (0.4%)	1/79 (1.3%)	1/78 (1.3%)	2/1030 (0.2%)	13/1038 (1.3%)
Injection Site Hematoma	1/466 (0.2%)	5/464 (1.1%)	36/506 (7.1%)	47/493 (9.5%)	8/172 (4.7%)	2/174 (1.1%)	36/1026 (3.5%)	57/1035 (5.5%)

Thrombocytopenia: See WARNINGS: Thrombocytopenia.

Other:

Allergic Reactions:

Allergic reactions (i.e., pruritus, rash, fever, injection site reaction, bullous eruption) and skin necrosis have occurred rarely. A few cases of anaphylactoid reactions have been reported.

Local Reactions:

Pain at injection site, the only non-bleeding event determined to be possibly or probably related to treatment with FRAGMIN and reported at a rate of at least 2% in the group treated with FRAGMIN, was reported in 4.5% of patients treated with FRAGMIN 5000 IU qd vs 11.8% of patients treated with heparin 5000 U bid in the abdominal surgery trials. In the hip replacement trials, pain at injection site was reported in 12% of patients treated with FRAGMIN 5000 IU qd vs 13% of patients treated with heparin 5000 U tid.

Ongoing Safety Surveillance:

Since first international market introduction in 1985, there have been five reports of epidural or spinal hematoma formation with concurrent use of dalteparin sodium and spinal/epidural anesthesia or spinal puncture. No cases have been reported in the United States since approval in 1994. Four of the five patients had post-operative indwelling epidural catheters placed for analgesia or

received additional drugs affecting hemostasis. The hematomas caused long-term or permanent paralysis in four of the cases (one complete, three partial paralyses). The fifth patient experienced temporary paraplegia but made a full recovery. Because these events were reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

OVERDOSAGE

Symptoms/Treatment:

An excessive dosage of FRAGMIN Injection may lead to hemorrhagic complications. These may generally be stopped by the slow intravenous injection of protamine sulfate (1% solution), at a dose of 1 mg protamine for every 100 anti-Xa IU of FRAGMIN given. A second infusion of 0.5 mg protamine sulfate per 100 anti-Xa IU of FRAGMIN may be administered if the APTT measured 2 to 4 hours after the first infusion remains prolonged. Even with these additional doses of protamine, the APTT may remain more prolonged than would usually be found following administration of conventional heparin. In all cases, the anti-Factor Xa activity is never completely neutralized (maximum about 60 to 75%).

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 100,000 IU/kg of FRAGMIN to mice caused a mortality of 8% (1/12) whereas 50,000 IU/kg was a non-lethal dose. The observed sign was hematoma at the site of injection.

DOSAGE AND ADMINISTRATION

Unstable Angina and Non-Q-wave Myocardial Infarction:

In patients with unstable angina or non-Q-wave myocardial infarction, the recommended dose of FRAGMIN Injection is 120 IU/kg of body weight, but not more than 10,000 IU, subcutaneously (s.c.) every 12 hours with concurrent oral aspirin (75-165 mg) therapy. Treatment should be continued until the patient is clinically stabilized. In clinical trials, the usual duration of treatment was 5 to 8 days. Concurrent aspirin therapy is recommended except when contraindicated.

Table 9 lists the volume of FRAGMIN to be administered for a range of patient weights.

Table 9

Volume of FRAGMIN to be Administered by Patient Weight

Patient weight (lb)	<110	110-131	132-153	154-175	176-197	≥198
Patient weight (kg)	<50	50-59	60-69	70-79	80-89	≥90
Fragmin volume (mL)*	0.55	0.65	0.75	0.90	1.00	1.00

* Calculated volume based on the 9.5 mL multiple dose vial (10,000 anti-Factor Xa IU/mL)

Hip Replacement Surgery:

In patients undergoing hip replacement surgery, the recommended first dose of FRAGMIN is 2500 IU administered by s.c. injection within 2 hours before surgery and the second dose of 2500 IU s.c. in the evening of the day of surgery (at least 6 hours after the first dose). If surgery is performed in the evening, omit the second dose on the day of surgery. Starting on the first postoperative day, the recommended dose of FRAGMIN is 5000 IU administered by s.c. injection once daily.

Alternatively, 5000 IU of FRAGMIN can be administered the evening before surgery, followed by 5000 IU once daily, starting in the evening of the day of surgery. Up to 14 days of treatment was well tolerated in controlled clinical trials, where the average duration of treatment was 5 to 10 days postoperatively.

Abdominal Surgery:

In patients undergoing abdominal surgery with a risk of thromboembolic complications, the recommended dose of FRAGMIN is 2500 IU administered by s.c. injection once daily, starting 1 to 2 hours prior to surgery and repeated once daily for 5 to 10 days postoperatively.

In patients undergoing abdominal surgery associated with a high risk of thromboembolic complications, such as malignant disorder, the recommended dose of FRAGMIN is 5000 IU s.c. the evening before surgery, then once daily for 5 to 10 days postoperatively. Alternatively, in patients with malignancy, 2500 IU of FRAGMIN can be administered s.c.

1 to 2 hours before surgery followed by 2500 IU s.c. 12 hours later, and then 5000 IU once daily for 5 to 10 days postoperatively.

Dosage adjustment and routine monitoring of coagulation parameters are not required if the dosage and administration recommendations specified above are followed.

Administration:

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

Subcutaneous injection technique: Patients should be sitting or lying down and FRAGMIN administered by deep s.c. injection. FRAGMIN may be injected in a U-shape area around the navel, the upper outer side of the thigh or the upper outer quadrangle of the buttock. The injection site should be varied daily. When the area around the navel or the thigh is used, using the thumb and forefinger, you **must** lift up a fold of skin while giving the injection. The entire length of the needle should be inserted at a 45 to 90 degree angle.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

HOW SUPPLIED

FRAGMIN Injection is available in the following strengths and package sizes:

0.2 mL single-dose prefilled syringe, affixed with a 27-gauge x 1/2 inch needle. Package of 10:

2500 anti-Factor Xa IU

NDC 0013-2406-91

5000 anti-Factor Xa IU

NDC 0013-2426-91

9.5 mL multiple-dose vial:

10,000 anti-Factor Xa IU/mL

NDC 0013-2436-06

(95,000 anti-Factor Xa IU/vial)

Store at controlled room temperature 20° to 25°C (68° to 77°F) [see USP].

Rx only

U.S. Patent 4,303,651

Manufactured for: Pharmacia & Upjohn Company
Kalamazoo, MI 49001, USA

By: Vetter Pharma-Fertigung
Ravensburg, Germany
(prefilled syringes)

Pharmacia & Upjohn AB
Stockholm, Sweden
(multiple-dose vial)

(Copy code) Revised _____