1. TRADE NAME(S) OF THE MEDICINAL PRODUCT

FRAGMIN ®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredient: dalteparin sodium

3. PHARMACEUTICAL FORM

Solution for Injection

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

1. Treatment of acute deep-vein thrombosis and pulmonary embolism.
2. Prevention of clotting in the extra corporeal system during hemodialysis and hemofiltration in patients with acute renal failure or chronic renal insufficiency.
3. Thromboprophylaxis in conjunction with surgery.
4. Thromboprophylaxis in patients with restricted mobility due to acute medical conditions.
5. Unstable coronary artery disease (unstable angina and non-ST-elevation myocardial infarction, also known as non-Q-wave myocardial infarction).
6. Extended treatment of symptomatic venous thromboembolism [VTE] (proximal deep-vein thrombosis and/or pulmonary embolism) to reduce the recurrence of VTE in patients with cancer.

4.2 Posology and Method of Administration

See *section 4.4* Special warnings and precautions for use

General - DO NOT ADMINISTER DALTEPARIN BY THE INTRAMUSCULAR ROUTE.

Compatibility with IV Solutions - Dalteparin is compatible with isotonic sodium chloride (9 mg/mL) or isotonic glucose (50 mg/mL) infusion solution in glass bottles and plastic containers.

1.) <u>Treatment of Acute Deep-vein Thrombosis and Pulmonary Embolism</u>

Administer dalteparin subcutaneously (SC) either as a single daily injection or as two daily injections. Simultaneous anticoagulation with oral vitamin-K antagonists can be started immediately. Continue combined treatment until the prothrombin complex tests have reached therapeutic levels (usually at least 5 days). Outpatient treatment is feasible using the same doses recommended for treatment in a medical institution.

- **Once daily administration -** 200 IU/kg total body weight SC once daily, up to a maximum of 18,000 IU. Monitoring of the anticoagulant effect is not necessary.

- **Twice daily administration -** Alternatively, a dose of 100 IU/kg total body weight administered SC twice daily may be given. Monitoring of the anticoagulant effect is generally not necessary but should be considered for specific patient populations (see ***section 4.4*** **Special warnings and precautions for use**). Samples should be taken during maximum plasma levels (3 to 4 hours after a SC injection). Recommended peak plasma levels are between 0.5 and 1.0 IU anti-Xa/mL.

2.) Prevention of Clotting in the Extra-corporeal System During Hemodialysis and Hemofiltration

Administer dalteparin intravenously (IV), selecting the appropriate regimen from those described below.

- **Patients with chronic renal insufficiency, or patients with no known risk of bleeding -** These patients normally require few dose adjustments, and therefore frequent monitoring of anti-Xa levels is not necessary for most patients. Recommended doses usually produce plasma levels between 0.5 to 1.0 IU anti-Xa/mL during dialysis.

- **Hemodialysis and hemofiltration up to a maximum of 4 hours -** Either 30 to 40 IU/kg total body weight IV bolus injection followed by 10 to 15 IU/kg/hour IV infusion, or a single IV bolus injection of 5000 IU.

- **Hemodialysis and hemofiltration longer than 4 hours -** Administer 30 to 40 IU/kg total body weight IV bolus injection, followed by 10 to 15 IU/kg/hour IV infusion.

- **Patients with acute renal failure, or patients with a high risk of bleeding -** Administer 5 to 10 IU/kg total body weight as IV bolus injection, followed by 4 to 5 IU/kg/hour IV infusion. Patients undergoing acute hemodialysis have a narrower therapeutic range than patients on chronic hemodialysis, and should undergo comprehensive monitoring of anti-Xa levels. Recommended plasma levels are between 0.2 to 0.4 IU anti-Xa/mL**.**

3.) Thromboprophylaxis in Conjunction with Surgery

Administer dalteparin subcutaneously (SC). Monitoring of the anticoagulant effect is generally not necessary. If done, samples should be taken during maximum plasma levels (3 to 4 hours after an SC injection). Recommended doses usually produce peak plasma levels between 0.1 and 0.4 IU anti-Xa/mL.

- **General surgery**
  Select the appropriate regimen from those listed below.

- **Patients at risk for thromboembolic complications -** 2500 IU SC within 2 hours before surgery and 2500 IU SC each postoperative morning until the patient is mobilized (generally 5 to 7 days or longer).

- **Patients with additional risk factors for thromboembolism (e.g. malignancy)** - Administer dalteparin until the patient is mobilized (generally 5 to 7 days or longer).

- **Start on day before surgery -** 5000 IU SC on the evening before surgery. Following surgery, 5000 IU SC each evening.

- **Start on day of surgery -** 2500 IU SC within 2 hours before surgery and 2500 IU SC 8 to 12 hours later, but no sooner than 4 hours after the end of surgery. Starting on the day after surgery, 5000 IU SC each morning.

- **Orthopedic surgery (such as hip replacement surgery) -** Administer dalteparin for up to 5 weeks after surgery, selecting one of the regimens listed below.

  - **Preoperative start: Evening before surgery -** 5000 IU SC on the evening before surgery. Following surgery, 5000 IU SC each evening.

  - **Preoperative start: Day of surgery -** 2500 IU SC within 2 hours before surgery and 2500 IU SC 8 to 12 hours later, but no sooner than 4 hours after the end of surgery. Starting on the day after surgery, 5000 IU SC each morning.

  - **Postoperative start -** 2500 IU SC 4 to 8 hours after surgery, but no sooner than 4 hours after the end of surgery. Starting on the day after surgery, 5000 IU SC each day.

4.) Thromboprophylaxis in Patients with Restricted Mobility

Administer 5000 IU of dalteparin subcutaneously (SC) once daily, generally for 12 to 14 days or longer in patients with continued restricted mobility. Monitoring of the anticoagulant effect is generally not necessary.

5.) Unstable Coronary Artery Disease (Unstable Angina and Non-ST-elevation Myocardial Infarction)

Administer dalteparin 120 IU/kg total body weight subcutaneously (SC) every 12 hours up to a maximum dose of 10,000 IU/12 hours. Unless specifically contraindicated, patients should also receive concomitant therapy with acetylsalicylic acid (75 to 325 mg/day).
Continue treatment until the patient is clinically stable (generally at least 6 days), or longer if considered of benefit by the physician. Thereafter, extended treatment with a fixed dose of dalteparin is recommended until a revascularization procedure is performed (such as percutaneous interventions [PCI] or coronary artery bypass graft [CABG]). The total treatment period should not exceed 45 days. The dose of dalteparin is selected according to the patient's gender and weight:

- For women weighing less than 80 kg and men weighing less than 70 kg, administer 5000 IU SC every 12 hours.
- For women weighing at least 80 kg and men weighing at least 70 kg, administer 7500 IU SC every 12 hours.

Monitoring of the anticoagulant effect is generally not necessary but should be considered for specific patient populations (see ***section 4.4*** **Special warnings and precautions for use**). Samples should be taken during maximum plasma levels (3 to 4 hours after a SC injection). Recommended peak plasma levels are between 0.5 and 1.0 IU anti-Xa/mL.

6.) Extended treatment of symptomatic VTE to reduce recurrence of VTE in patients with cancer

- **Month 1**
  Administer dalteparin 200 IU/kg total body weight subcutaneously (SC) once daily for the first 30 days of treatment. The total daily dose should not exceed 18,000 IU daily.

- **Months 2-6**
  Dalteparin should be administered at a dose of approximately 150 IU/kg subcutaneously, once daily using fixed dose syringes and the Table 1 shown below.

Table 1: Dosage determination for months 2-6

Body Weight (kg)	Dalteparin Dose (IU)
≤56	7500
57 to 68	10,000
69 to 82	12,500
83 to 98	15,000
≥99	18,000

Dose reductions for chemotherapy-induced thrombocytopenia:

Thrombocytopenia - In the case of chemotherapy-induced thrombocytopenia with platelet counts <50,000/mm^3, dalteparin should be interrupted until the platelet count recovers above 50,000/mm^3.

For platelet counts between 50,000 and 100,000/mm^3, dalteparin should be reduced by 17% to 33% of the initial dose depending on the patient's weight (**Table 2**). Once the platelet count recovered to ≥100,000/mm^3, dalteparin should be re-instituted at full dose.

Table 2: Dose Reduction of Dalteparin for Thrombocytopenia 50,000-100,000/mm^3

Body Weight (kg)	Scheduled Dalteparin Dose (IU)	Reduced Dalteparin Dose (IU)	Mean Dose Reduction (%)
≤56	7500	5000	33
57 to 68	10,000	7500	25
69 to 82	12,500	10,000	20
83 to 98	15,000	12,500	17
≥99	18,000	15,000	17

Renal failure - In the case of significant renal failure, defined as a creatinine level >3 x ULN, the dose of dalteparin should be adjusted to maintain an anti-Xa therapeutic level of 1 IU/mL (range 0.5-1.5 IU/mL) measured 4-6 hours after the dalteparin injection. If the anti-Xa level is below or above the therapeutic range, the dose of dalteparin should be increased or reduced, respectively, by one syringe formulation and the anti-Xa measurement should be repeated after 3-4 new doses. This dose adjustment is to be repeated until the anti-Xa therapeutic level is achieved.

Pediatric population

The safety and efficacy of dalteparin sodium in children has not been established. Currently available data are described in sections 5.1 and 5.2 but no recommendation on a posology can be made.

Monitoring Anti-Xa levels in children

Measurement of peak anti-Xa levels at about 4 hours post-dose should be considered for certain special populations receiving dalteparin sodium, such as children. For therapeutic treatment with doses administered once daily, peak anti-Xa levels should generally be maintained between 0.5 and 1.0 IU/mL measured at 4 hours post-dose. In the case of low and changing physiologic renal function such as in neonates, close monitoring of anti-Xa levels is warranted. For prophylaxis treatment the anti-Xa levels should generally be maintained between 0.2-0.4 IU/mL.

As with all antithrombotic agents, there is a risk of systemic bleeding with dalteparin sodium administration. Care should be taken with dalteparin sodium use in high dose treatment of newly operated patients. After treatment is initiated patients should be carefully monitored for bleeding complications. This may be done by regular physical examination of the patients, close observation of the surgical drain and periodic measurements of hemoglobin, and anti-Xa determinations.

4.3 Contraindications

Dalteparin should not be used in patients who have:

- Confirmed or suspected history of immunologically-mediated heparin-induced thrombocytopenia,
- Active, clinically-significant bleeding (such as gastrointestinal ulceration or bleeding, or cerebral hemorrhage),
- Severe coagulation disorders,
- Acute or sub-acute septic endocarditis,
- Recent injury to, or surgical procedures of, the central nervous system, eyes and/or ears,
- Hypersensitivity to dalteparin, or other low molecular weight heparins, or heparins, or pork products.
- Because of an increased risk of bleeding, concomitant treatment with high doses of dalteparin (such as those needed to treat acute deep-vein thrombosis, pulmonary embolism, and unstable coronary artery disease) should not be used in patients who will receive spinal or epidural anesthesia or other procedures requiring spinal puncture (see ***section 4.4*** **Special warnings and precautions for use**).

4.4 Special Warnings and Precautions for Use

Epidural or Spinal Anesthesia

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 nonsteroidal 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 monitored frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment (spinal cord decompression) is necessary (see ***section 4.3*** **Contraindications**).

Insertion or removal of the epidural or spinal catheter should be postponed to 10-12 hours after dalteparin doses administered for thrombosis prophylaxis, while in those receiving higher therapeutic dalteparin doses (such as 100 IU/kg -120 IU/kg every 12 hours or 200 IU/kg once daily), the interval should be a minimum of 24 hours. Extreme vigilance and frequent monitoring must be exercised to detect any signs and symptoms of neurologic impairment such as back pain, sensory or motor deficits (numbness and weakness in lower limbs) and bowel or bladder dysfunction.

Risk of Hemorrhage

Dalteparin should be used with caution in patients who have a potentially higher risk of hemorrhage, such as patients with thrombocytopenia, platelet disorders, severe liver or kidney insufficiency, uncontrolled hypertension, or hypertensive or diabetic retinopathy. High doses of dalteparin, such as those needed to treat deep-vein thrombosis, pulmonary embolism, or unstable coronary artery disease, should be used with caution in patients who had a recent surgical procedure.

Thrombocytopenia

It is recommended that the platelets be counted before the initiation of dalteparin treatment and be followed regularly during treatment. Special caution is necessary if thrombocytopenia develops rapidly or to a significant degree (less than 100,000/μL or mm^3) during treatment with dalteparin. In either case, an in vitro test for antiplatelet antibodies in the presence of heparins or low molecular weight heparins is recommended. If the result of the in vitro test is positive or inconclusive, or no test is performed, treatment with dalteparin should be stopped (see ***section 4.3*** **Contraindications**).

Monitoring Anti-Xa Levels

Monitoring of the anticoagulant effect of dalteparin is generally not necessary but should be considered for specific patient populations such as pediatrics; those with renal failure; or those who are very thin or morbidly obese, pregnant, or at increased risk for bleeding or rethrombosis. Laboratory assays using a chromogenic substrate are considered the method of choice for measuring anti-Xa levels. Activated Partial Thromboplastin Time (APTT) or thrombin time should not be used because these tests are relatively insensitive to the activity of dalteparin. Increasing the dose of dalteparin in an attempt to prolong APTT may result in bleeding (see ***section 4.9*** **Overdose).**

Hyperkalemia

Heparin and low molecular weight heparin can suppress adrenal secretion of aldosterone leading to hyperkalaemia, particularly in patients such as those with diabetes mellitus, chronic renal failure, pre-existing metabolic acidosis, raised plasma potassium or taking potassium sparing drugs. Plasma potassium should be measured in patients at risk.

Interchangeability With Other Anticoagulants

Dalteparin cannot be used interchangeably (unit for unit) with unfractionated heparin, other low molecular weight heparins, or synthetic polysaccharides. Each of these medicines differ in their starting raw materials, manufacturing process, physico-chemical, biological, and clinical properties, leading to differences in biochemical identity, dosing, and possibly clinical efficacy and safety. Each of these medicines is unique and has its own instructions for use.

Osteoporosis

Long term treatment with heparin has been associated with a risk of osteoporosis. Although this has not been observed with dalteparin the risk of osteoporosis cannot be excluded.

Pediatric Patients

There is limited safety and efficacy information on the use of dalteparin in pediatric patients. If dalteparin is used in these patients, anti-Xa levels should be monitored.

Geriatric Patients

Elderly patients (especially patients aged eighty years and above) may be at an increased risk for bleeding complications within the therapeutic dosage ranges. Careful clinical monitoring is advised.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of drugs affecting hemostasis, such as thrombolytic agents, other anticoagulants, nonsteroidal anti-inflammatory drugs, or platelet inhibitors, or dextran, may enhance the anticoagulant effect of dalteparin (see ***section 4.2*** **Posology and method of administration - Unstable Coronary Artery Disease (Unstable Angina and Non-ST-elevation Myocardial Infarction)).**

Because NSAIDs and ASA analgesic/anti-inflammatory doses reduce production of vasodilatatory prostaglandins, and thereby renal blood flow and the renal excretion, particular care should be taken when administering dalteparin concomitantly with NSAIDs or high dose ASA in patients with renal failure.

4.6 Pregnancy and lactation

Pregnancy - If dalteparin is used during pregnancy, the possibility of fetal harm appears remote. However, because the possibility of harm cannot be completely ruled out, dalteparin should be used during pregnancy only if clearly needed (see ***section 5.3*** **Preclinical safety data).**

A large amount of data on pregnant women (more than 1000 exposed outcomes) indicate no malformative nor feto/ neonatal toxicity. Dalteparin sodium can be used during pregnancy if clinically needed.

There are more than 2,000 published cases (studies, case series and case reports) on administration of dalteparin in pregnancy. As compared with unfractionated heparin, a lower bleeding tendency and reduced risk of osteoporotic fracture was reported. The largest prospective study “Efficacy of Thromboprophylaxis as an Intervention during Gravidity” (EThIG), involved 810 pregnant women and investigated a pregnancy-specific scheme for risk stratification (low, high, very high risk of venous thromboembolism) with daily doses of dalteparin between 50 – 150 IU/kg body weight (in single cases up to max. 200 IU/kg body weight). However, only limited randomized controlled studies are available on the use of low molecular weight heparins in pregnancy.

Animal experiments did not show any teratogenic or fetotoxic properties of dalteparin (see ***section 5.3*** **Preclinical safety data**).

Caution is recommended when treating patients with an increased risk of haemorrhage, such as perinatal women (see ***section 4.4*** **Special warnings and precautions for use**).

Therapeutic failures have been reported in pregnant women with prosthetic heart valves on full anti-coagulant doses of low molecular weight heparin. Dalteparin has not been adequately studied for use in pregnant women with prosthetic heart valves.

Lactation - Limited data are available for excretion of dalteparin in human milk. One study in 15 lactating women receiving prophylactic doses of dalteparin detected small amounts of anti-Xa activity in breast milk, equivalent to a milk/plasma ratio of <0.025-0.224. As oral absorption of low molecular weight heparin is extremely low the clinical implications, if any, of this small amount of anticoagulant activity on the nursing infant are unknown.

Fertility - Based on current clinical data there is no evidence that dalteparin sodium affects fertility. No effects on fertility, copulation or peri- and postnatal development were noted when dalteparin sodium was tested in animals.

4.7 Effects on ability to drive and use machines

The effect of dalteparin on the ability to drive or use machinery has not been systematically evaluated.

4.8 Undesirable Effects

About 3% of the patients having had prophylactic treatment reported side-effects.

The reported adverse reactions, which may possibly be associated to dalteparin sodium, are listed in the following table by system organ class and frequency group: *very common* (≥1/10), *common* (≥1/100 to <1/10), *uncommon* (≥1/1000 to <1/100), *rare* (≥1/10,000 to <1/1000), *very rare* (<1/10,000).

System Organ Class	*Frequency*	*Adverse reactions*
Blood and Lymphatic System Disorders	Common	Mild thrombocytopenia (type I), which usually is reversible during the treatment
	Not Known*	Immunologically-mediated heparin-induced thrombocytopenia (type II, with or without associated thrombotic complications)
Immune System Disorders	Uncommon	Hypersensitivity
	Not Known*	Anaphylactic reactions
Nervous System Disorders	Not Known*	Intracranial bleeds have been reported and some have been fatal
Vascular Disorders	Common	Haemorrhage
Gastrointestinal Disorders	Not Known*	Retroperitoneal bleeds have been reported and some have been fatal
Hepatic and Biliary Disorders	Common	Transient elevation of transaminases
Skin and Subcutaneous Tissue Disorders	Rare	Skin necrosis, transient alopecia
	Not Known*	Rash

General Disorders and Administration Site Conditions	Common	Subcutaneous haematoma at the injection site Pain at the injection site
Injury, Poisoning and Procedural Complications	Not Known*	Spinal or epidural hematoma (see ***section 4.3*** **Contraindications** and ***section 4.4*** **Special warnings and precautions for use**)

*(cannot be established from available data)

Pediatric population:
Frequency, type and severity of adverse reactions in children are expected to be the same as in adults. The safety of long term dalteparin administration has not been established.

4.9 Overdose

The anticoagulant effect induced by dalteparin may be inhibited by protamine. However, protamine has an inhibiting effect on primary hemostasis and should be used only in an emergency. A dose of 1 mg of protamine partially neutralizes the effect of 100 IU (anti-Xa) of dalteparin (although the induced prolongation of the clotting time is fully neutralized, 25 to 50% of the anti-Xa activity of dalteparin remains).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

The antithrombotic effect of dalteparin is due to its ability to intensify the inhibition of factor Xa and thrombin. Dalteparin has, from the general aspect, greater ability to intensify the inhibition of factor Xa than to prolong the time for clot formation in plasma (APTT). Dalteparin has a relatively small effect on platelet function and platelet adhesiveness compared with heparin and thereby a small effect on primary hemostasis.

In a large international randomized, controlled multi-center study, entitled PROTECT (PROphylaxis for ThromboEmbolism in Critical Care Trial), the thromboprophylactic effect of dalteparin 5,000 IU once daily was compared to unfractionated heparin (UFH) 5,000 IU twice daily in 3746 critically ill medical (76%) and surgical patients who were admitted in the intensive care unit (ICU) for at least 3 days. The primary outcome was proximal leg deep vein thrombosis (DVT) as determined by periodic compression ultrasound. Approximately 90% of the patients required mechanical ventilation. Treatment with the study drug was allowed for the duration of ICU stay to a maximum of 90 days. The median duration of study drug in both groups was 7 days (interquartile range, 4 to 12). A blinded adjudication of thrombotic and bleeding events was performed.

There was no significant difference in proximal leg DVT between the two groups (5.1% in the dalteparin group and 5.8% in the UFH group, hazard ratio 0.92; 95% CI, 0.68 to 1.23; P=0.57).

A significant 49% risk reduction in the secondary end-point of pulmonary embolism (PE) was seen with dalteparin (absolute difference 1.0%; 95% CI 0.30 to 0.88; P=0.01).

There was no significant differences between the two groups in the rates of major bleeding (hazard ratio, 1.00; 95% CI, 0.75 to 1.34; P = 0.98) or death in the hospital (hazard ratio, 0.92; 95% CI, 0.80 to 1.05; P = 0.21).

Pediatric population:
There is limited safety and efficacy information on the use of dalteparin in pediatric patients. If dalteparin is used in these patients, anti-Xa levels should be monitored.

The largest prospective study investigated the efficacy, safety and relation of dose to plasma anti-Xa activity of dalteparin in prophylaxis and therapy of arterial and venous thrombosis in 48 pediatric patients.

Table 3 Nohe at al (1999) Study Demographics and Trial Design

Trial Design	Patients	Diagnosis	Indication, Dalteparin Sodium Dose, Target anti-Xa, Duration		
Single-center, open label trial; (n = 48)	Age: 31 week preterm to 18 years Gender: 32 males, 16 females	Arterial or venous thrombosis; PVOD; PPH	Prophylaxis: (n = 10) 95 ± 52 anti-Xa IU/kg sc qd; 0.2 to 0.4 IU/mL 3-6 months	Primary Therapy: (n = 25) 129 ± 43 anti-Xa IU/kg sc qd; 0.4 to 1.0 IU/mL 3-6 months	Secondary Therapy: (n = 13) 129 ± 43 anti-Xa IU/kg sc qd; 0.4 to 1.0 IU/mL 3-6 months

In this study, no thromboembolic events occurred in the 10 patients receiving dalteparin for thromboprophylaxis. In the 23 patients given dalteparin for primary antithrombotic therapy of arterial or venous thrombosis, complete recanalization was seen in 7/23 (30%), partial recanalization in 7/23 (30%) and no recanalization in 9/23 (40%). In the 8 patients administered dalteparin for secondary antithrombotic therapy following successful thrombolysis, recanalization was maintained or improved. In the 5 patients receiving dalteparin for secondary therapy following failed thrombolysis, no recanalization was seen. Minor bleeding, reported in 2/48 children (4%), resolved after dose reduction. Patient platelet counts ranged from 37,000/µl to 574,000/µl. The authors attributed platelet counts below normal (150,000/µl) to immunosuppressive therapy. A reduction in platelet count ≥50% of the initial value, a sign of heparin-induced thrombocytopenia type 2 (HIT 2), was not observed in any patient. For both prophylaxis and therapy groups, the dalteparin doses (anti-Xa IU/kg) required to achieve target anti-Xa activities (IU/ml) were inversely related to age ($r^2 = 0.64$, $P = 0.017$; $r^2 = 0.13$, $P = 0.013$).

The predictability of the anticoagulant effect with weight-adjusted doses appears to be reduced in children compared to adults, presumably due to altered plasma binding (see ***section 5.2*** **Pharmacokinetic Properties**).

5.2 Pharmacokinetic Properties

Pharmacokinetics and Metabolism

Absorption - Absolute bioavailability in healthy volunteers, measured as the anti-Factor Xa activity, was 87 ± 6%. Increasing the dose from 2500 to 10,000 IU resulted in an overall increase in anti-Factor Xa AUC that was proportionally greater by about one-third.

Distribution - The volume of distribution for dalteparin anti-Factor Xa activity was 40 to 60 mL/kg.

Metabolism - 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.

Excretion - Dalteparin is primarily excreted by the kidneys, however, the biological activity of the renally eliminated fragments is not well characterized. Less than 5% of anti-Xa activity is detectable in the urine. 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.

Special Populations

Hemodialysis - 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 dalteparin 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.

Pediatric Population:
Infants less than approximately 2 to 3 months of age or <5 kg have increased LMWH requirements per kg likely due to their larger volume of distribution. Alternative explanations for the increased requirement of LMWH per body weight in young children include altered heparin pharmacokinetics and/or a decreased expression of anticoagulant activity of heparin in children due to decreased plasma concentrations of antithrombin.

5.3 Preclinical Safety Data

Carcinogenesis, Mutagenesis, Impairment of Fertility - Irrespective of method of administration, dose or treatment period, no organotoxicity was noted. No mutagenic effects were noted. No embryotoxic, fetotoxic or teratogenic effects, and no effects on fertility, copulation or peri- and postnatal development were noted when tested in animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients :
Sodium chloride, hydrochloric acid or sodium hydroxide to adjust pH, and water for injection.

6.2 Incompatibilities
No reported

6.3 Shelf Life
36 months

6.4 Special Precautions for Storage

Store below 30°C .
"All medications should be kept out of reach of children"

6.5 Nature and Contents of Container

External container / secondary: Folding carton
Internal container / mediate: Plastic Blister PVC / PAPER
Internal container / immediate / primary: Syringe Type I colorless glass, rubber stopper, plunger of polypropylene, stainless steel needle.
Presentation:
Fragmin 2500 UI anti Xa/0.2 mL: Box x 10 syringes prefilled of 0.2 mL
Fragmin 5000 UI anti Xa/0.2 mL: Box x 10 syringes prefilled of 0.2 mL

6.6 Special Precautions for Disposal and Other Handling

N/A

Manufacturer by: Vetter Pharma Fertigung GMBH & CO. KG., Ravensburg - Alemania

Imported and distributed by: Pfizer Cía Ltda., Quito Ecuador

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