FRAGMIN®

Dalteparin Sodium
Solution for Injection

1. NAME 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 (DVT)

2. Prevention of clotting in the extracorporeal system during hemodialysis and hemofiltration in patients with acute renal failure or chronic renal insufficiency

3. Thromboprophylaxis in conjunction with surgery

4. The prophylaxis of proximal DVT in patients bedridden due to a medical condition, including, but not limited to: congestive cardiac failure, acute respiratory failure or acute infection, who also have a predisposing risk factor for venous thromboembolism such as age over 75 years, obesity, cancer or previous history of VTE

5. Unstable coronary artery disease (unstable angina and non-ST-elevation myocardial infarction, also known as non-Q-wave myocardial infarction)

Dalteparin should not be used in patients who have suffered a recent (within 3 months) stroke unless due to systemic emboli.

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.

Dalteparin is administered by subcutaneous injection for all indications except for the prevention of clotting in the extracorporeal system during hemodialysis and hemofiltration where it is administered either intravenously or into the arterial side of the dialyzer.

Compatibility with Intravenous (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.

The solution should be used within 12 hours.

1. Treatment of Acute DVT

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 (3-4 hours after an SC injection). Recommended peak plasma levels are between 0.5 and 1.0 IU anti-Factor Xa/mL.

2. Prevention of Clotting in the Extracorporeal System During Hemodialysis and Hemofiltration

Administer dalteparin into the arterial side of the dialyzer or intravenously, 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-Factor Xa levels is not necessary for most patients.

    - **Hemodialysis and hemofiltration up to a maximum of 4 hours -** A single bolus injection of 5,000 IU can be administered, either intravenously or into the arterial side of the extracorporeal system, at the start of the procedure. Alternatively, administer 30 to 40 IU/kg total body weight IV bolus injection, followed by 10 to 15 IU/kg/h IV infusion.

      The 5,000 IU starting dose for the single bolus dosing regimen can be adjusted, session-to-session, based on the outcome of the previous dialysis; the dose may be increased or decreased in steps of 500 or 1,000 anti-Factor Xa IU until a satisfactory outcome is obtained (see ***section 5.1.* Pharmacodynamic properties**).

    - **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/h 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/h IV infusion. Patients undergoing acute hemodialysis have a narrower therapeutic range than patients on chronic hemodialysis, and should undergo comprehensive monitoring of anti-Factor Xa levels. Recommended plasma levels are between 0.2 and 0.4 IU anti-Factor Xa/mL.

3. <u>Thromboprophylaxis in Conjunction with Surgery</u>

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

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

- **Patients at risk for thromboembolic complications -** Administer 2,500 IU SC within 2 hours before surgery and 2,500 IU SC each postoperative morning until the patient is mobilized (generally 5-7 days or longer).

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

    - **Start on day before surgery -** 5,000 IU SC on the evening before surgery; following surgery, 5,000 IU SC each evening.

    - **Start on day of surgery -** 2,500 IU SC within 2 hours before surgery and 2,500 IU SC 8 to 12 hours later, but no sooner than 4 hours after the end of surgery; starting on the day after surgery, 5,000 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 -** 5,000 IU SC on the evening before surgery; following surgery, 5,000 IU SC each evening.

    - **Preoperative start: Day of surgery -** 2,500 IU SC within 2 hours before surgery and 2,500 IU SC 8 to 12 hours later, but no sooner than 4 hours after the end of surgery; starting on the day after surgery, 5,000 IU SC each morning.

    - **Postoperative start -** 2,500 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, 5,000 IU SC each day.

4. <u>Thromboprophylaxis in Patients with Restricted Mobility</u>

Administer 5,000 IU of dalteparin 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. <u>Unstable Coronary Artery Disease (Unstable Angina and Non-ST-elevation Myocardial Infarction)</u>

Administer dalteparin 120 IU/kg total body weight SC every 12 hours up to a maximum dose of 10,000 IU/12 h. Unless specifically contraindicated, patients should also receive concomitant therapy with acetylsalicylic acid (75-325 mg/day). Continue treatment until the patient is clinically stable (generally at least 6 days), or longer if considered of benefit by the physician.

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 (3-4 hours after an SC injection). Recommended peak plasma levels are between 0.5 and 1.0 IU anti-Factor Xa/mL.

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, other low molecular weight heparins (LMWH), 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 DVT 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

There have been no adequate studies to assess the safe and effective use of dalteparin in preventing valve thrombosis in patients with prosthetic heart valves. Prophylactic doses of dalteparin are not sufficient to prevent valve thrombosis in patients with prosthetic heart valves. The use of dalteparin cannot be recommended for this purpose.

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 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 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 to 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 DVT, pulmonary embolism (PE) or unstable coronary artery disease, should be used with caution in patients who had a recent surgical procedure.

The concomitant use with drugs affecting hemostasis, such as thrombolytic agents, oral anticoagulants, NSAIDs, platelet inhibitors, or dextran may enhance the anticoagulant effect of dalteparin and is not recommended. Appropriate caution should be exercised under specific circumstances of switching anticoagulant therapy (see ***section 4.5.*** **Interaction with other medicinal products and other forms of interaction**).

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-Factor 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-Factor 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 hyperkalemia, 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 (UFH), other low molecular weight heparins, or synthetic polysaccharides. Each of these medicines differs in its 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-Factor Xa levels should be monitored.

The preservative benzyl alcohol has been associated with serious adverse events, including the “gasping syndrome”, and death in pediatric patients. Although normal therapeutic doses of this product ordinarily deliver amounts of benzyl alcohol that are substantially lower than those reported in association with the “gasping syndrome”, the minimum amount of benzyl alcohol at which toxicity may occur is not known. The risk of benzyl alcohol toxicity depends on the quantity administered and the liver and kidneys’ capacity to detoxify the chemical. Premature and low-birth weight infants may be more likely to develop toxicity.

Because benzyl alcohol may cross the placenta, dalteparin multiple-dose vials, preserved with benzyl alcohol, should be used with caution in pregnant women and only if clearly needed (see ***section 4.6.*** **Fertility, pregnancy and lactation**).

Benzyl alcohol containing formulations must not be used in premature or newborn babies. Benzyl alcohol may cause toxic reactions and anaphylactoid reactions in infants and children up to 3 years old (see ***section 6.1.*** **List of excipients**). Other formulations without benzyl alcohol are available.

Geriatric Patients

Elderly patients (especially patients aged 80 years and above) may be at an increased risk for bleeding complications within the therapeutic dosage ranges. Careful clinical monitoring is advised.

Allergic Reactions

The needle shield of Fragmin prefilled syringes may contain latex (natural rubber) which may cause severe allergic reactions in individuals with hypersensitivity to latex (natural rubber).

4.5. Interaction with other medicinal products and other forms of interaction

Concomitant use of drugs affecting hemostasis, such as thrombolytic agents, other oral anticoagulants, NSAIDs, 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)** and ***4.4.*** **Special warnings and precautions for use - Risk of Hemorrhage**).

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

4.6. Fertility, 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 1,000 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 to UFH, a lower bleeding tendency and reduced risk of osteoporotic fracture were 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 VTE) with daily doses of dalteparin between 50 and 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 hemorrhage, 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 anticoagulant doses of low molecular weight heparin. Dalteparin has not been adequately studied for use in pregnant women with prosthetic heart valves.

Medications Containing Benzyl Alcohol

See ***section 4.4*****. Special warnings and precautions for use - Pediatric Patients**.

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-Factor Xa activity in breast milk, equivalent to a milk/plasma ratio of <0.025 to 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 post-natal 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 following table lists adverse drug reactions (ADRs) within each standard system organ class (SOC) and CIOMS frequency category, ranked by decreasing order of medical seriousness:

System Organ Class	Very Common ≥1/10	Common ≥1/100 to <1/10	Uncommon ≥1/1,000 to <1/100	Rare ≥1/10,000 to <1/1,000	Very Rare <1/10,000	Frequency Not Known (cannot be estimated from the available data)
Blood and lymphatic system disorders		Mild thrombocytopenia[a]				Immunologically mediated heparin-induced thrombocytopenia[b,*]
Immune system disorders			Hypersensitivity			Anaphylactic reactions*
Metabolism and nutrition disorders		Hyperkalemia				
Nervous system disorders						Intracranial bleeds[c,*]
Vascular disorders		Hemorrhage				
Gastrointestinal disorders						Retroperitoneal bleeds[d,*]
Hepatobiliary disorders		Transient elevation of liver transaminases				
Skin and subcutaneous tissue disorders				Transient alopecia, skin necrosis		Rash*
General disorder and administration site conditions		Pain at the injection site, subcutaneous hematoma at the injection site				
Injury, poisoning and procedural complications						Spinal or epidural hematoma* (see ***sections 4.3.*** **Contraindications** and ***4.4.*** **Special warnings and precautions for use**)

[a] Mild thrombocytopenia (Type I), which is usually reversible during treatment.
[b] Immunologically mediated heparin-induced thrombocytopenia (Type II, with or without associated thrombotic complications).
[c] Intracranial bleeds have been reported and some have been fatal.
[d] Retroperitoneal bleeds have been reported and some have been fatal.
* ADR identified post-marketing.

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 sodium 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-Factor Xa) of dalteparin (although the induced prolongation of the clotting time is fully neutralized, 25%-50% of the anti-Factor 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 to 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 UFH 5,000 IU twice daily in 3,746 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 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 4-12). 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 0.68-1.23; P = 0.57).

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

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

Parrot Study (A6301091): A phase IIIb open-label study in adults aged 18 to 85 years that allowed flexible dosing with increment/decrement of 500 or 1,000 IU following standard dalteparin sodium 5,000 IU bolus to optimize treatment for the prevention of clotting within the extracorporeal system during hemodialysis procedures for subjects with chronic renal insufficiency.

Subjects had been previously treated with UFH or LMWH and had end-stage renal failure requiring 3 or 4 hemodialysis sessions each of 4 hours or less per week.

Table 1: Study Demographics and Trial Design

Diagnosis	**Dalteparin Dosage, Route of Administration and Duration**	**Study Subjects**
Subjects with end-stage renal failure requiring 3 or 4 hemodialysis sessions (for	5,000 IU single bolus dose given into the arterial side of the dialyzer at the start of the procedure. This dose could be adjusted by	152 subjects

4 hours or less) per week, with no other known risks of bleeding.	increment/decrement of 500 IU or 1,000 IU, at the discretion of the investigator. Criteria for dose adjustments were occurrence of clotting grade 3 or 4, minor bleeding during hemodialysis or between hemodialysis sessions, prolonged access compression time (>10 minutes) or other clinical events. Study duration for a maximum of 20 hemodialysis sessions.	enrolled and treated. Gender: 106 males, 46 females

The mean proportion of successful hemodialysis sessions (defined as a hemodialysis session which was completed as planned, without the need for premature termination due to clotting in the hemodialysis circuit) was 99.9% (2,774 of 2,776 evaluable hemodialysis sessions; 50 hemodialysis sessions were excluded from the analysis because the effect of dalteparin sodium could not be assessed), with a 95% CI of 99.7% to 100.0%. No hemodialysis session was prematurely terminated due to a safety event of bleeding.

For subjects who completed at least one hemodialysis session, the dalteparin dose was adjusted for 79 (52.3%) subjects, and 72 (47.7%) subjects received the standard fixed dose of 5,000 IU per hemodialysis session at all hemodialysis sessions.

There was no evidence of bioaccumulation of anti-Factor Xa serum levels. Only for 2 subjects, the pre-hemodialysis session value was above the threshold of <0.4 IU/mL at hemodialysis session 10 but this was resolved at hemodialysis session 20.

The results of this study demonstrate that a flexible dosing regimen of dalteparin sodium administered into the arterial side of the extracorporeal system during hemodialysis sessions up to 4 hours in subjects with chronic renal failure and no other known risks of bleeding is effective and well tolerated, and that a flexible dosing regimen is appropriate to address the potential limitations of the fixed dose regimen (5,000 IU).

Overall, an adjustable dalteparin sodium dose regimen allowed safe completion of hemodialysis, with clinical benefits over fixed dosing.

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-Factor Xa levels should be monitored.

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

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 eight patients

administered dalteparin for secondary antithrombotic therapy following successful thrombolysis, recanalization was maintained or improved. In the five 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.

The predictability of the anticoagulant effect with weight-adjusted doses appears to be reduced in children compared to adults, presumably due to altered pharmacokinetics (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 2,500 IU 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 mL/kg to 60 mL/kg.

Metabolism

Following IV doses of 40 IU/kg and 60 IU/kg, mean terminal half-lives were 2.1 ± 0.3 h and 2.3 ± 0.4 h, respectively. Longer apparent terminal half-lives (3-5 hours) are observed following SC 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-Factor Xa activity is detectable in the urine. The mean plasma clearances of dalteparin anti-Factor Xa activity in normal volunteers following single IV bolus doses of 30 anti-Factor Xa IU/kg and 120 anti-Factor Xa IU/kg were 24.6 ± 5.4 and 15.6 ± 2.4 mL/h/kg, respectively. The corresponding mean disposition half-lives are 1.47 ± 0.3 h and 2.5 ± 0.3 h, respectively.

Special Populations

Hemodialysis

In patients with chronic renal insufficiency requiring hemodialysis, the mean terminal half-life of anti-Factor Xa activity following a single IV dose of 5,000 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

The pharmacokinetics of twice-daily SC dalteparin, measured as anti-Factor Xa activity, was characterized in 89 pediatric subjects with or without cancer from two clinical studies and 1 observational study. Dalteparin pharmacokinetics (PK) were described by a 1-compartment model with linear absorption and elimination and PK parameters are shown in Table 2. After correcting for the body weight, clearance (CL/F) decreased with increasing age, while volume of distribution at steady-state (V_d/F) remained similar. The mean elimination half-life increased with age.

Table 2: Pharmacokinetic Parameters of Dalteparin in Pediatric Population

Parameter	Birth to <8 weeks	≥8 weeks to <2 years	≥2 years to <8 years	≥8 years to <12 years	≥12 years to <19 years
Median Age (range) (years)	0.06 (0.04-0.14)	0.5 (0.2-1.91)	4.47 (2.01-7.6)	9.62 (8.01-10.5)	15.9 (12.0-19.5)
Derived Mean (SD) CL/F (mL/h/kg)	55.8 (3.91)	40.4 (8.49)	26.7 (4.75)	22.4 (3.40)	18.8 (3.01)
Derived Mean (SD) V_d/F (mL/kg)	181 (15.3)	175 (55.3)	160 (25.6)	165 (27.3)	171 (38.9)
Derived Mean (SD) $t_{½\beta}$(h)	2.25 (0.173)	3.02 (0.688)	4.27 (1.05)	5.11 (0.509)	6.28 (0.937)

CL = clearance; F = absolute bioavailability; SD = standard deviation; $t_{½\beta}$ = elimination half-life; V_d = volume of distribution.

5.3. Preclinical safety data

Carcinogenesis, Mutagenesis, Impairment of Fertility

The acute toxicity of dalteparin sodium is considerably lower than that of heparin. The only significant finding, which occurred consistently throughout the toxicity studies after SC administration of the higher doses was local hemorrhage at the injection site, dose-related in incidence and severity. There was no cumulative effect on injection site hemorrhages.

The hemorrhagic reaction was reflected in dose related changes in the anticoagulant effects as measured by APTT and anti-Factor Xa activities.

It was concluded that dalteparin sodium did not have a greater osteopenic effect than heparin since at equivalent doses the osteopenic effect was comparable.

The results revealed no organ toxicity irrespectively of the route of administration, doses or the duration of treatment. No mutagenic effect was found. No embryotoxic or teratogenic effects and no effect on fertility, reproductive capacity or peri- and postnatal development were shown.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sodium chloride
Water for injections
Sodium hydroxide
Hydrochloric acid

The drug product contains no preservative and is for single use only.

6.2. Incompatibilities

None stated.

6.3. Shelf life

Refer to shelf life statement on outer carton.

6.4. Special precautions for storage

Store below 30°C.

6.5. Nature and contents of container

Type I glass vial.

Each vial contains 4 mL of dalteparin sodium at a concentration of 2,500 IU (anti-Factor Xa) per mL, and there are 10 vials per carton.

Potency is described in international anti-Factor Xa units (IU) of the 1st International Standard for Low Molecular Weight Heparin.

7. PRODUCT OWNER

Pfizer Inc
New York,
United States

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