PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

Pr ARIXTRA®

fondaparinux sodium injection

2.5 mg/0.5 mL
5.0 mg/0.4 mL
7.5 mg/0.6 mL
10.0 mg/0.8 mL

ATC Classification: B01AX05

Synthetic Antithrombotic

Intravenous or Subcutaneous

Aspen Pharmacare Canada Inc.
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Date of Initial Approval:
July 19, 2002

Date of Preparation:
July 19, 2019

Submission Control No: 225665

TABLE OF CONTENTS

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

ARIXTRA® (fondaparinux sodium, injection) is indicated for:

- Prophylaxis of venous thromboembolic events (VTE) for up to one month post-surgery in patients undergoing orthopedic surgeries of the lower limbs such as hip fracture, knee surgery or hip replacement surgery.
- Prophylaxis of venous thromboembolic events (VTE) in patients undergoing abdominal surgery who are at high risk of thromboembolic complications, such as patients undergoing abdominal cancer surgery.
- Treatment of Acute Deep Vein Thrombosis (DVT) and treatment of Acute Pulmonary Embolism (PE).
- Management of unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI) for the prevention of death and subsequent myocardial infarction.
- Management of ST segment elevation myocardial infarction (STEMI) for the prevention of death and myocardial reinfarction in patients who are managed with thrombolytics or who initially are to receive no form of reperfusion therapy.

1.1 Pediatrics

Pediatrics (< 17 years of age): No data are available to Health Canada; therefore, Health Canada has not
authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (> 65 years of age): ARIXTRA® should be used with caution in elderly patients due to the risk of hemorrhage.

2 CONTRAINDICATIONS

ARIXTRA® is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see Dosage Forms, Strengths, Composition and Packaging.

- Thrombocytopenia associated with a positive *in vitro* test for anti-platelet antibody in the presence of fondaparinux sodium.
- Active clinically significant bleeding.
- Acute bacterial endocarditis.

3 DOSAGE AND ADMINISTRATION

3.1 Dosing Considerations

Use in Patients with Renal Insufficiency
The risk of hemorrhage increases with increasing renal insufficiency. ARIXTRA® should be used with caution in patients with moderate renal insufficiency (creatinine clearance 30–50 mL/min) (see ACTION AND CLINICAL PHARMACOLOGY, Renal Insufficiency). In severe renal impairment, the use of ARIXTRA® should be avoided or, if the physician determines that the benefit outweighs the risk, ARIXTRA® should only be used with caution.

Renal function should be assessed periodically in patients receiving the drug. For prophylactic use following orthopedic surgery, ARIXTRA® should be discontinued immediately in patients who develop severe renal insufficiency or labile renal function while on therapy. After discontinuation of ARIXTRA®, its anticoagulant effects may persist for 2-4 days in patients with normal renal function (i.e. at least 3-5 half-lives). The anticoagulant effects of ARIXTRA® may persist even longer in patients with renal insufficiency.

Use in Patients with Hepatic Insufficiency
No dose adjustment is recommended in patients with mild to moderate hepatic impairment, based upon single-dose pharmacokinetic data. Pharmacokinetic data are not available for patients with severe hepatic impairment. Patients with hepatic impairment may be particularly vulnerable to bleeding during ARIXTRA® therapy. Observe these patients closely for signs and symptoms of bleeding (see WARNINGS AND PRECAUTIONS).

Use in Pediatric Patients
Health Canada has not authorized an indication for pediatric (<17 years of age) use.

Use in Geriatric Patients
Use with caution in elderly patients (see WARNINGS AND PRECAUTIONS, Geriatrics, and ADVERSE REACTIONS, Geriatrics).

Use in Patients with Low Body Weight
For patients of body weight < 50 kg, ARIXTRA® should be used with caution (see WARNINGS AND PRECAUTIONS, Low Body Weight).

3.2 Recommended Dose and Dosage Adjustment

Prophylaxis of VTE following orthopedic surgery
The recommended dose of ARIXTRA® (fondaparinux sodium) is 2.5 mg once daily administered post-operatively by subcutaneous injection.

After hemostasis has been established, the initial dose should be given no earlier than 6 hours after surgical closure. In clinical studies, 99% of the patients had received the initial dose of ARIXTRA® by 18 hours after surgical closure. **Administration before 6 hours after orthopedic surgery has been associated with an increased risk of major bleeding**. The

timing of the first dose of ARIXTRA® following surgery requires strict adherence (see WARNING AND PRECAUTIONS, Hemorrhage, and Peri-Operative Considerations; ACTION AND CLINICAL PHARMACOLOGY).

The usual duration of prophylactic therapy with ARIXTRA® is 7 ± 2 days. Treatment should be continued for as long as the risk of VTE persists. In patients for whom extended prophylaxis is indicated, administration of ARIXTRA® in or out of the hospital up to an additional 24 days is recommended. In clinical trials of extended prophylaxis, a total of 32 days (peri-operative and extended prophylaxis) has been tolerated.

Prophylaxis of VTE following abdominal surgery
The recommended dose of ARIXTRA® is 2.5 mg once daily administered post-operatively by subcutaneous injection after hemostasis has been established.

The initial dose should be given 6 to 8 hours after surgery. **Administration before 6 hours after abdominal surgery has been associated with an increased risk of major bleeding.** The timing of the first dose of ARIXTRA® following surgery requires strict adherence (see WARNING AND PRECAUTIONS, Hemorrhage, and Peri-Operative Considerations; ACTION AND CLINICAL PHARMACOLOGY).

The usual duration of administration is 5 to 9 days, and up to 10 days of ARIXTRA® injection has been administered.

Treatment of DVT and PE
The recommended dose of ARIXTRA® is 5 mg (body weight < 50 kg), 7.5 mg (body weight 50-100 kg) or 10 mg (body weight > 100 kg) by subcutaneous injection once daily.

Concomitant oral anticoagulation treatment should be initiated as soon as possible, usually within 72 hours. ARIXTRA® injection treatment should be continued for at least 5 days and until a therapeutic oral anticoagulant effect is established (INR 2.0 to 3.0).

The average duration of administration is 7 days. In controlled clinical trials administration of ARIXTRA® injection for up to 26 days to a small number of patients has been well tolerated.

Management of Unstable Angina/Non-ST Segment Elevation Myocardial Infarction (UA/NSTEMI)
The recommended dose of ARIXTRA® is 2.5 mg once daily, administered by subcutaneous injection. Treatment should be initiated as soon as possible following diagnosis and may be continued for up to 8 days or until hospital discharge.

If a patient is to undergo percutaneous coronary intervention (PCI) while being treated with ARIXTRA®, an effective anti-thrombin regimen such as unfractionated heparin (UFH) should be administered as an adjunct to PCI, as per standard practice, taking into account the patient's potential risk of bleeding, including the time since the last dose of ARIXTRA® (see WARNINGS AND PRECAUTIONS, Risk of catheter thrombosis during PCI, and Hemorrhage).

The timing of the next dose of subcutaneous ARIXTRA® after sheath removal should be based on clinical judgment. In the UA/NSTEMI clinical trials treatment with ARIXTRA® was restarted no earlier than 2 hours after sheath removal.

In patients who are to undergo coronary artery bypass graft (CABG) surgery, ARIXTRA® where possible, should not be given during the 24 hours before surgery and may be restarted 48 hours post-operatively.

Management of ST Segment Elevation Myocardial Infarction (STEMI)

The recommended dose of ARIXTRA® is 2.5 mg once daily. The first dose of ARIXTRA® is administered intravenously and subsequent doses are administered by subcutaneous injection. Treatment should be initiated as soon as possible following diagnosis and continued for up to 8 days or until hospital discharge.

ARIXTRA® should not be used if primary PCI is the planned reperfusion therapy (see INDICATIONS, WARNINGS AND PRECAUTIONS, Risk of catheter thrombosis during PCI). ARIXTRA® is indicated for use in patients who are managed with thrombolytics or who initially are to receive no form of reperfusion therapy.

If a patient is to undergo subsequent PCI while being treated with ARIXTRA®, an effective anti-thrombin regimen such as unfractionated heparin (UFH) should be administered as an adjunct to PCI as per standard practice, taking into account the patient's potential risk of bleeding, including the time since the last dose of ARIXTRA® (see WARNINGS AND PRECAUTIONS, Risk of catheter thrombosis during PCI, and Hemorrhage).

There are limited data on the use of UFH during non-primary PCI in STEMI patients treated with fondaparinux (see CLINICAL TRIALS). In those patients with STEMI who underwent non-primary PCI in OASIS-6 less than 6 hours after the last dose of fondaparinux, the median dose of UFH was 5000 IU and the incidence of major bleeding was 4.1% (2/49). In those patients who underwent non-primary PCI 6-24 hours after the last dose of fondaparinux, the median dose of UFH was 8000 IU and the incidence of major bleeding was 2% (2/98).

The timing of the next dose of subcutaneous fondaparinux after sheath removal should be based on clinical judgment. In the STEMI clinical trials treatment with fondaparinux was restarted no earlier than 3 hours after sheath removal.

In patients who are to undergo coronary artery bypass graft (CABG) surgery, fondaparinux where possible, should not be given during the 24 hours before surgery and may be restarted 48 hours post-operatively.

Health Canada has not authorized an indication for pediatric (<17 years of age) use. (see Indications, Pediatrics)

3.3 Administration

ARIXTRA® is intended for use under a physician's guidance. Patients may self-inject only if their physician determines that it is appropriate, and with medical follow-up as necessary. Proper training in subcutaneous injection technique should be provided.

Subcutaneous administration:
Administration is by subcutaneous injection only. **Do not inject ARIXTRA® intramuscularly.**

To avoid the loss of medicinal product when using the pre-filled syringe do not expel the air bubble from the syringe before the injection. For step-by-step instructions for use, please see CONSUMER INFORMATION.

Intravenous administration:
For STEMI patients treated with ARIXTRA®, the initial dose is to be administered intravenously. Administration should be through an existing intravenous line either directly or using a small volume (25 mL or 50 mL) 0.9% saline minibag as the first dose in the treatment of STEMI.

To avoid the loss of medicinal product when using the pre-filled syringe, do not expel the air bubble from the syringe before the injection. The intravenous tubing should be well flushed with saline after the administration of ARIXTRA® injection to ensure that all of the medicinal product is administered. If administered via a minibag, the infusion should be given over 1 to 2 minutes.

If ARIXTRA® is added to a 0.9% saline minibag it should be infused immediately, but can be stored between 15-30°C for up to 24 hours. Minibags are typically composed of a variety of polymers including PVC, polyethylene, polypropylene, or styrene-ethylene-butadiene, individually or in combination.

In the absence of compatibility studies, ARIXTRA® must not be mixed with other medicinal products.

3.4 Missed Dose

Never inject a double dose to make up for forgotten individual doses. The management depends on clinical judgement.

4 OVERDOSAGE

Hemorrhage is the major clinical sign of overdosage.
Overdosage of ARIXTRA® (fondaparinux sodium), associated with bleeding complications, should lead to treatment discontinuation, a search for the primary cause of bleeding, and initiation of appropriate therapy, which may include surgical hemostasis, blood replacement, fresh plasma transfusion, or plasmapheresis.

Minor bleeding rarely requires specific therapy, and reducing or delaying subsequent doses of ARIXTRA® (fondaparinux sodium) is usually sufficient.

For management of a suspected drug overdose, contact your regional poison control centre.

5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging.

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Subcutaneous	Injection/ 2.5 mg/0.5 mL 5.0 mg/0.4 mL 7.5 mg/0.6 mL 10.0 mg/0.8 mL	Isotonic solution of sodium chloride, water for injection and if necessary, sodium hydroxide or hydrochloric acid for pH adjustment.
Intravenous	Injection/ 2.5 mg/0.5 mL	

ARIXTRA® (fondaparinux sodium) injection, supplied as a sterile injectable solution for subcutaneous and intravenous use, is available in the following strengths and package sizes:

Package of 10:
2.5 mg ARIXTRA® in pre-filled 0.5 mL single use syringe, affixed with a 27-gauge x ½ inch needle with a blue plunger within a built-in automatic needle protection.

5 mg* ARIXTRA® in 0.4 mL single use pre-filled syringe, affixed with a 27-gauge x ½ inch needle with an orange plunger within a built-in automatic needle protection.

7.5 mg ARIXTRA® in 0.6 mL single use pre-filled syringe, affixed with a 27-gauge x ½ inch needle with a magenta plunger within a built-in automatic needle protection.

10 mg* ARIXTRA® in 0.8 mL single use pre-filled syringe, affixed with a 27-gauge x ½ inch needle with a violet plunger within a built-in automatic needle protection.

As with all parenteral drug products, syringes should be inspected visually for clarity, particulate matter, precipitate, discolouration and leakage prior to administration. Solutions showing haziness, particulate matter, precipitate, discolouration or leakage should not be used.

* *Strengths not available in Canada*.

6 WARNINGS AND PRECAUTIONS

General

ARIXTRA® (fondaparinux sodium) must be administered only by the subcutaneous (SC) or intravenous (IV) route. **ARIXTRA® must not be administered intramuscularly.**

Latex Allergy: The needle shield of the pre-filled syringe contains dry natural latex rubber that has the potential to cause allergic reactions in latex sensitive individuals.

Carcinogenesis and Mutagenesis
See TOXICOLOGY, Carcinogenicity and Mutagenicity.

Cardiovascular
Risk of catheter thrombosis during PCI

In patients undergoing any percutaneous coronary intervention (PCI), the use of ARIXTRA® as the sole anticoagulant during PCI is not recommended because of an increased risk of guiding catheter thrombosis. An effective anti-thrombin regimen such as unfractionated heparin (UFH) should be used as an adjunct to PCI, according to standard practice (see DOSAGE AND ADMINISTRATION, and DETAILED PHARMACOLOGY).

In STEMI patients undergoing primary PCI for reperfusion, the use of ARIXTRA® prior to and during PCI is not recommended (see ADVERSE REACTIONS, *Management of STEMI*, Risk of catheter thrombosis during PCI, and DOSAGE AND ADMINISTRATION).

Clinical trials have shown a low but increased risk of guiding catheter thrombosis in patients treated solely with ARIXTRA® for anticoagulation during PCI compared to control (see ADVERSE REACTIONS, *Management of UA/NSTEMI* and *Management of STEMI*, Risk of catheter thrombosis during PCI). Incidences during PCI in UA/NSTEMI were 1.00% with ARIXTRA®, 0.32% with enoxaparin alone, and 0.16% with enoxaparin with adjunctive UFH. In fondaparinux-treated UA/NSTEMI patients randomized to receive one of two dosing regimens of adjunctive UFH during PCI, the incidences of catheter thrombus were reported to range from 0.1% to 0.5%, depending on the UFH dose administered (For further details, see ADVERSE REACTIONS, *Management of UA/NSTEMI*, Risk of catheter thrombosis during PCI). In patients with STEMI undergoing primary PCI, incidences were 1.18% with ARIXTRA® and 0% with UFH. Use of ARIXTRA® during primary PCI is not recommended.

It is to be expected that the risk of peri-procedural myocardial infarction (MI) may be increased in patients who develop guiding catheter thrombosis, irrespective of anticoagulant used (see ADVERSE REACTIONS, *Management of UA/NSTEMI* and *Management of STEMI*, Risk of catheter thrombosis during PCI).

Driving and Operating Machinery
Due caution should be exercised when driving or operating a vehicle or potentially dangerous machinery.

Hematologic
Hemorrhage
ARIXTRA®, like other antithrombotic drugs, should be used with caution in patients who have an increased risk of hemorrhage, such as those with congenital or acquired bleeding disorders, active ulcerative gastrointestinal disease and recent intracranial hemorrhage or shortly after brain, spinal, or ophthalmological surgery.

Risk of hemorrhage is expected to increase with decreasing renal function (see ADVERSE REACTIONS). Appropriate caution should be exercised in patients with moderate to severe renal impairment (see WARNINGS AND PRECAUTIONS, Renal).

Prophylaxis and Treatment of VTE
Agents that may enhance the risk of hemorrhage, with the exception of vitamin K antagonists used concomitantly for treatment of VTE, should be discontinued prior to initiation of ARIXTRA® therapy. If co-administration is necessary, close monitoring may be appropriate (see DRUG INTERACTIONS).

Prophylaxis of VTE following orthopedic or abdominal surgery (timing of first fondaparinux injection)
The timing of the first dose of ARIXTRA® following surgery requires strict adherence. The first dose should be given no earlier than 6 hours following surgical closure, and only after hemostasis has been established. Administration before 6 hours has been associated with an increased risk of major bleeding (see DOSAGE and ADMINISTRATION). Patient groups at particular risk are those older than 75 years of age, body weight of less than 50 kg or renal impairment with creatinine clearance less than 50 mL/min.

Management of UA/NSTEMI, STEMI
ARIXTRA® should be used with caution in patients who are being treated concomitantly with other therapies that increase the risk of hemorrhage (such as GPIIb/IIIa inhibitors or thrombolytics).

Thrombocytopenia
Thrombocytopenia of any degree should be monitored closely. If the platelet count falls below 50,000/mm3, ARIXTRA® should be discontinued. ARIXTRA® is contraindicated in patients with thrombocytopenia associated with a positive *in vitro* test for anti-platelet antibody in the presence of fondaparinux.

Rare spontaneous reports of heparin-induced thrombocytopenia (HIT) in patients treated with fondaparinux have been received.

Prophylaxis of VTE following orthopedic or abdominal surgery
Thrombocytopenia can occur with the administration of ARIXTRA® following any major surgical procedure. Moderate thrombocytopenia (platelet counts between 100,000/mm^3 and 50,000/mm^3) occurred at a rate of 3.0% in patients given ARIXTRA® 2.5 mg in the peri-operative orthopedic and abdominal surgery clinical trials. Severe thrombocytopenia (platelet counts less than 50,000/ mm^3) occurred at a rate of 0.2% in patients given 2.5 mg in peri-operative clinical trials.

Treatment of DVT and PE
Moderate thrombocytopenia occurred at a rate of 0.5% in patients given the ARIXTRA® treatment regimen in the DVT and PE treatment clinical trials. Severe thrombocytopenia

occurred at a rate of 0.04% in patients given the ARIXTRA® treatment regimen.

Hepatic
There is no evidence that fondaparinux is metabolized or eliminated hepatically. Following a single subcutaneous dose of 7.5 mg of ARIXTRA® in patients with moderate hepatic impairment (Child-Pugh Category B) compared to subjects with normal liver function, changes from baseline in aPTT, PT/INR, and antithrombin III were similar in the two groups (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Hepatic Insufficiency). However, a higher incidence of hemorrhage was observed in subjects with moderate hepatic impairment than in normal subjects, especially mild hematomas at the blood sampling or injection site. The pharmacokinetics of fondaparinux have not been studied in patients with severe hepatic impairment. The use of ARIXTRA® should be considered with caution because of an increased risk of bleeding due to a deficiency of coagulation factors in patients with severe hepatic insufficiency. Thus, in patients with severe hepatic insufficiency, ARIXTRA® should be used only with care.

Monitoring, Laboratory and Coagulation Tests
Since the international standards of heparin or low molecular weight heparins (LMWH) are not appropriate calibrators, the activity of fondaparinux sodium is expressed in milligrams (mg) of the fondaparinux and cannot be compared with activities of heparin or LMWH.

At the 2.5 mg dose, ARIXTRA® does not have a clinically relevant effect on routine coagulation tests such as activated partial thromboplastin time (aPTT), activated clotting time (ACT) or prothrombin time (PT)/International Normalized Ratio (INR) tests in plasma. When administered at the recommended prophylactic dose, routine coagulation tests such as PT and aPTT are relatively insensitive measures of ARIXTRA® activity, and therefore unsuitable for monitoring. Although monitoring of ARIXTRA® is generally not required, the anti-Factor Xa assay is the preferred test to measure the anti-coagulant activity of ARIXTRA®. Only fondaparinux can be used to calibrate the anti-Xa assay (see ACTION AND CLINICAL PHARMACOLOGY, Mechanism of Action).

If during ARIXTRA® therapy, unexpected changes in coagulation parameters or major bleeding occurs, ARIXTRA® should be discontinued and a search for other causes such as concomitant medications that could interfere with coagulation, should be undertaken.

Peri-Operative Considerations
There have been cases of intra-spinal hematomas with the concurrent use of antithrombotics (i.e. low molecular weight heparins) and spinal/epidural anaesthesia resulting in long-term or permanent paralysis. The risk of these events may be higher with the use of post-operative indwelling epidural catheters or by the concomitant use of drugs affecting hemostasis: nonsteroidal anti-inflammatory drugs (NSAIDS), platelet inhibitors, or other drugs affecting coagulation. The risk also appears to be increased by traumatic or repeated epidural or spinal procedure. **ARIXTRA® should only be used concurrently with spinal/epidural anaesthesia when the therapeutic benefits to the patients outweigh the possible risks.** Careful vigilance for neurological signs is recommended with rapid diagnosis and treatment, if signs occur.

Renal
The plasma clearance of fondaparinux decreases with the severity of renal impairment, and is associated with an increased risk of hemorrhage (see ACTION AND CLINICAL PHARMACOLOGY, Renal Insufficiency). This has also been observed with all low molecular weight heparins (LMWH).

In patients with severe renal impairment, i.e., creatinine clearance (CrCl) < 30 mL/min, use of ARIXTRA should generally be avoided, due to increased risk of bleeding (see DOSAGE AND ADMINISTRATION, *Use in Patients with Renal Insufficiency*).

Prophylaxis of VTE following orthopedic or abdominal surgery
Occurrences of major bleeding in patients receiving prophylactic therapy following orthopedic surgery with normal renal function, mild renal insufficiency, moderate renal insufficiency and severe renal insufficiency have been found to be 1.6% (25/1565), 2.4% (31/1288), 3.8% (19/504) and 4.8% (4/83) respectively.

Major bleeding in patients receiving prophylactic therapy in abdominal surgery in an active-controlled trial with dalteparin sodium, occurred in 2.1% (13/606) of patients with normal renal function, in 3.6% (22/613) with mild renal impairment, in 6.7% (12/179) with moderate renal impairment, and in 7.1% (1/14) with severe renal impairment.

Therefore, ARIXTRA® prophylactic therapy following orthopedic or abdominal surgery is not recommended in patients with severe renal insufficiency (CrCl < 30 mL/min) and should be used with caution in patients with moderate renal insufficiency (CrCl 30-50 mL/min) (see ACTION AND CLINICAL PHARMACOLOGY, Renal Insufficiency).

Renal function should be assessed periodically in orthopedic and abdominal surgery patients receiving prophylactic therapy. Consideration of immediate discontinuation of ARIXTRA® should be undertaken for patients who develop severe renal insufficiency or labile renal function while on prophylactic therapy. After discontinuation of ARIXTRA® prophylactic therapy, its anticoagulant effects may persist for 2-4 days in patients with normal renal function (i.e. at least 3-5 half-lives). The anticoagulant effects of ARIXTRA® prophylactic therapy may persist even longer in patients with renal insufficiency.

Treatment of DVT and PE
No dosing adjustment is generally necessary in patients with mild to moderate renal insufficiency, however, close monitoring of these patients is recommended. In patients with severe renal impairment (creatinine clearance ≤ 30 mL/min) use is not recommended due to risk of hemorrhage.

Management of UA/NSTEMI, STEMI
There are limited clinical data available on the use of fondaparinux 2.5 mg once daily in patients with creatinine clearance ≤ 30 mL/min (see DOSAGE AND ADMINISTRATION, and ACTION AND CLINICAL PHARMACOLOGY, Renal Insufficiency).

6.1 Special Populations

Low Body Weight
Patients with body weight < 50 kg are at increased risk of bleeding due to reduced clearance of ARIXTRA.

Prophylaxis of VTE following orthopedic or abdominal surgery
ARIXTRA® prophylactic therapy should be used with caution in patients with body weight < 50 kg undergoing orthopedic surgery.

Treatment of DVT and PE
For DVT and PE treatment, in patients with body weight < 50 kg, a daily dose of 5 mg is recommended. In patients with body weight > 100 kg, a daily dose of 10 mg is recommended (see DOSAGE AND ADMINISTRATION).

Management of UA/NSTEMI, STEMI
ARIXTRA® should be used with caution in patients weighing < 50 kg.

6.1.1 Pregnant Women

There are very limited clinical data available on the use of ARIXTRA® in pregnant women. Caution should be exercised when prescribing ARIXTRA® to pregnant women. ARIXTRA® should not be prescribed to pregnant women unless the potential benefit outweighs the risk. Animal studies do not indicate either direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or post-natal development (see TOXICOLOGY).

6.1.2 Breast-feeding

Although it is not known whether fondaparinux is excreted in human milk, it has been shown to be excreted in the milk of lactating rat dams. Because many drugs may be excreted in human milk, breast feeding is not recommended during treatment with ARIXTRA®.

6.1.3 Pediatrics

6.1.4 No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.Geriatrics

Geriatrics (> 65 years of age): ARIXTRA® should be used with caution in elderly patients because of increased risk of hemorrhage (see ADVERSE REACTIONS). Since fondaparinux sodium is substantially excreted by the kidney, risks associated with its use may be expected to be greater in patients with impaired renal function, including the elderly (see ADVERSE REACTIONS, and DOSAGE AND ADMINISTRATION). Because elderly patients are more likely to have decreased renal function, renal function should be monitored, as clinically warranted (see WARNINGS AND PRECAUTIONS, Renal).

7 ADVERSE REACTIONS

7.1 Clinical Trial Adverse Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates*.

The data described below reflect experience in over 25,000 patients randomized to ARIXTRA® (fondaparinux sodium) Injection in controlled trials of hip fracture, hip replacement, major knee, or abdominal surgeries, treatment of DVT and PE, and the management of UA/NSTEMI and STEMI. Patients received ARIXTRA® primarily in two large peri-operative dose-response trials (n=989), four active-controlled peri-operative VTE prophylaxis trials with enoxaparin sodium (n=3,616), an extended VTE prophylaxis trial (n=327), an active-controlled VTE prophylaxis trial with dalteparin sodium (n=1,425) in abdominal surgery, a dose-response trial (n=111) and an active-controlled trial with enoxaparin sodium in DVT treatment (n=1,091), an active-controlled trial with heparin in PE treatment (n=1,092), an active-controlled trial (OASIS 5) with enoxaparin in the treatment of UA/NSTEMI (n=9,979), and an active and placebo-controlled trial (OASIS 6) with standard of care in the treatment of STEMI (n=5,954), (see CLINICAL TRIALS).

Additionally, safety data were obtained from the FUTURA/OASIS 8 trial, comparing two adjunctive UFH regimens during non-primary PCI in UA/NSTEMI patients treated with ARIXTRA® (n=2,026).

Hemorrhage
As with any antithrombotic treatment, hemorrhagic manifestations can occur. In clinical trials or in post-marketing experience, rare cases of intracranial/ intracerebral or retroperitoneal bleedings have been reported.

Prophylaxis of VTE following orthopedic surgery
The rates of major bleeding events reported during the orthopedic surgery clinical trials with ARIXTRA® 2.5 mg injection are provided in Table 1, Table 2 and Table 3 below.

Table 1 Summary of Bleeding Results From First Injection Up to Day 11 – Percentage of Patients

Surgery Type		Bleeding	ARIXTRA® 2.5 mg daily (%)	Enoxaparin (%)
Hip Fracture		Major bleeding[1]	18/831 (2.2)	19/842 (2.3)
		Minor bleeding[2]	34/831 (4.1)	18/842 (2.1)
Knee Replacement		Major bleeding	11/517 (2.1[5])	1/517 (0.2)
		Minor bleeding	14/517 (2.7)	19/517 (3.7)
Hip Replacement	Study 1[4]	Major bleeding	20/1128 (1.8)	11/1129 (1.0)
		Minor bleeding	17/1128 (1.5)	24/1129 (2.1)
	Study 2[3]	Major bleeding	47/1140 (4.1)	32/1133 (2.8)
		Minor bleeding	44/1140 (3.9)	38/1133 (3.4)

[1] Major bleeding was defined as clinically overt bleeding that was (1) fatal, (2) at a critical site (e.g. Intracranial, retroperitoneal, intra-ocular, pericardial, spinal or into adrenal gland), (3) associated with re-operation or (4) Bleeding Index (BI) ≥ 2 i.e. BI = drop in hemoglobin (Hb) pre-bleed minus post-bleed + number of units transfused. There were no fatal bleeds or bleeds at a critical site in the ARIXTRA® group, and one fatal bleed and one bleed into a critical site in the enoxaparin group.

[2] Minor bleeding was clinically overt bleeding that was not major.

[3] Comparator was Enoxaparin 40 mg o.d.

[4] Comparator was Enoxaparin 30 mg b.i.d.

[5] p-value versus enoxaparin is 0.0081.

Table 2 Bleeding Across Hip Fracture, Hip Replacement and Knee Replacement Surgery Studies

	ARIXTRA® 2.5 mg SC once daily	**Comparator: Enoxaparin Sodium[1]**
	N = 3616	**N = 3956**
Major bleeding[2]	96 (2.7%)	75 (1.9%)
Fatal bleeding	0 (0.0%)	1 (< 0.1%)
Non-fatal bleeding at critical site	0 (0.0%)	1 (< 0.1%)
Re-operation due to bleeding	12 (0.3%)	10 (0.3%)
Bleeding Index (BI) ≥ 2[3,5]	84 (2.3%)	63 (1.6%)
Minor bleeding[4]	109 (3.0%)	116 (2.9%)

1 Enoxaparin Sodium dosing regimen: 30 mg every 12 hours or 40 mg once daily (see Clinical Trials).

2 Major bleeding was defined as clinically overt bleeding that was (1) fatal, (2) bleeding at critical site (e.g. intracranial, retroperitoneal, intra-ocular, pericardial, spinal or into adrenal gland), (3) associated with reoperation at operative site, or (4) with a bleeding index (BI) ≥ 2.

3 BI ≥ 2: overt bleeding associated only with a bleeding index ≥ 2 [calculated as number of whole blood or packed red blood cells units transfused + [(pre-bleeding) - (post-bleeding)] hemoglobin (g/dL) values].

4 Minor bleeding was defined as clinically overt bleeding that was not major.

5 Incidence of BI ≥ 2 with ARIXTRA® across the 4 phase III studies decreased when the first dose was given ≥ 6 hours after surgical closure.

Table 3 Number (Percentage) of Patients With Adjudicated Bleeding Events in Hip Fracture Surgery

	Pre-randomization Open-Label Period (Day 1 to Day 7 ± 1 post-surgery)	Randomized Double-Blind Extended Prophylaxis Period (Day 8 to Day 28 ± 2 post-surgery)	
	ARIXTRA® N = 737	ARIXTRA® N = 327	Placebo N = 329
Any bleeding	37 (5.0%)	13 (4.0%)	4 (1.2%)
Minor bleeding only[1]	15 (2.0%)	5 (1.5%)	2 (0.6%)
Any major bleeding[2]	22 (3.0%)	8 (2.4%)	2 (0.6%)
Fatal bleeding	2 (0.3%)	0 (0.0%)	0 (0.0%)
Non-fatal bleeding	1 (0.1%)	0 (0.0%)	0 (0.0%)
Other non-fatal major bleeding	19 (2.6%)	8 (2.4%)	2 (0.6%)
At surgical site leading to re-operation	3 (0.4%)	2 (0.6%)	2 (0.6%)
Only bleeding index (BI) ≥ 2[3]	16 (2.2%)	6 (1.8%)	0 (0.0%)

1 Minor bleeding was defined as clinically overt bleeding that was not major.
2 Major bleeding was defined as clinically overt bleeding that was (1) fatal, (2) bleeding at critical site (e.g. intracranial, retroperitoneal, intra-ocular, pericardial, spinal or into adrenal gland), (3) associated with reoperation at operative site, or (4) with a bleeding index (BI) ≥ 2.
3 Adjudicated as major and with BI ≥ 2 and/or decrease of hemoglobin ≥ 2 g/dL and/or number of units transfused ≥ 2.

Major bleeding from the first active ARIXTRA® dose decreased by 26% if the first dose was given 6 hours after surgical closure: major bleeding with ARIXTRA® started < 6 hours after surgical closure was 2.6% (n=1,337) versus major bleeding with ARIXTRA® started 6 hours after surgical closure which was 1.9% (n=2,230).

Geriatrics: Over 2,300 patients, 65 years and older, have received ARIXTRA® 2.5 mg in randomized clinical trials in the orthopedic surgery program. In the peri-operative, orthopedic surgery, clinical trials with patients receiving ARIXTRA® 2.5 mg, the risk of ARIXTRA®-associated non-fatal major bleeding increased with age: 1.8% (23/1,253) in patients < 65 years, 2.2% (24/1,111) in those 65-74 years, and 2.7% (33/1,227) in those ≥ 75 years. Serious adverse events increased with age for patients receiving ARIXTRA®. In patients undergoing extended prophylaxis following the first week of therapy, the incidence of ARIXTRA®-associated non-fatal major bleeding was: 1.9% (1/52) in patients < 65 years, 1.4% (1/71) in those 65-74 years, and 2.9% (6/204) in those ≥ 75 years.

Prophylaxis of VTE following abdominal surgery
The rates of major bleeding reported during an abdominal surgery clinical trial with ARIXTRA® 2.5 mg are provided in Table 4 below.

Table 4 Major and Non-Major Bleeding Episodes[1] in a Randomized, Controlled, Abdominal Surgery Study

	Study 1	
	ARIXTRA® 2.5 mg SC once daily	**Dalteparin Sodium 5,000 IU SC once daily**
	N = 1433	**N = 1425**
Major bleeding[1]	49 (3.4%)	34 (2.4%)
Fatal bleeding	2 (0.1%)	2 (0.1%)
Non-fatal bleeding at critical site	0 (0.0%)	0 (0.0%)
Other non-fatal major bleeding Surgical site Non-surgical site	 38 (2.7%) 9 (0.6%)	 26 (1.8%) 6 (0.4%)
Minor bleeding[2]	31 (2.2%)	23 (1.6%)

[1] Major bleeding was defined as bleeding that was (1) fatal, (2) bleeding at the surgical site leading to intervention, (3) non-surgical bleeding at a critical site (eg. intracranial, retroperitoneal, intra-ocular, pericardial, spinal, or into adrenal gland), or leading to an intervention, and/or with a bleeding index (BI ≥2 calculated as [number of whole blood or packed red blood cell unites transfused + [(pre-bleeding) – (post-bleeding)] hemoglobin (g/dL) values]).

[2] Minor bleeding was defined as clinically overt bleeding that was not major.

Geriatrics: In the abdominal surgery active-controlled clinical trial with dalteparin sodium, the risk of major bleeding associated with use of ARIXTRA® increased with age: 3.0% (19/644) in patients < 65 years, 3.2% (16/507) in those 65-74 years, and 5.0% (14/282) in those ≥ 75 years.

Treatment of DVT and PE

The rates of major bleeding events reported during the DVT and PE clinical trials with the ARIXTRA® injection treatment regimen are provided in Table 5 below.

Table 5 Major Bleeding Episodes[1,2] in DVT and PE Treatment Studies

Indications	ARIXTRA® Treatment Regimen	Enoxaparin Sodium[1] mg/kg SC q 12h	Heparin IV aPTT adjusted
	N = 2294	N = 1101	N = 1092
DVT and PE Treatment	28 (1.2%)	13 (1.2%)	12 (1.1%)

[1] Major bleeding was defined as clinically overt - and/or contributing to death - and/or in a critical organ including intracranial, retroperitoneal, intraocular, spinal, pericardial or adrenal gland - and/or associated with a fall in hemoglobin level = 2 g/dL - and/or leading to a transfusion ≥ 2 units of packed red blood cells or whole blood.

[2] Bleeding rates are during the study drug treatment period (approximately 7 days). Patients were also treated with vitamin K antagonists initiated within 72 hours after the first study drug administration.

Geriatrics: Over 1,200 patients, 65 years and older, have received the ARIXTRA® treatment regimen in the DVT and PE treatment clinical trials. In the DVT and PE treatment clinical trials with patients receiving the ARIXTRA® treatment regimen, the risk of ARIXTRA®-associated non-fatal major bleeding increased with age: 0.6% (7/1,151) in patients < 65 years, 1.6% (9/560) in those 65-74 years, and 2.1% (12/583) in those ≥ 75 years. Careful attention to dosing directions and concomitant medications (especially antiplatelet medication) is advised (see DRUG INTERACTIONS).

Management of UA/NSTEMI

The rates of major bleeding events reported during the management of UA/NSTEMI clinical trials with ARIXTRA® 2.5 mg injection are provided in Table 6 and Table 7 below.

Table 6 Bleeding Episodes in OASIS 5, a Randomized, Controlled Study in UA/NSTEMI[5]

	Up to 9 days after presenting with UA/NSTEMI	
	ARIXTRA®[5] N = 9979	**Enoxaparin[6]** N = 9969
Investigator Reported Major Bleeding[1]	205 (2.1%)	410 (4.1%)
Fatal bleeding	7 (<0.1%)	22 (0.2%)
Intracranial	7 (<0.1%)	7 (<0.1%)
Retroperitoneal	9 (<0.1%)	36 (0.4%)
Requiring surgical intervention	39 (0.4%)	78 (0.8%)
Drop in hemoglobin ≥ 3 g/dL	189 (1.9%)	385 (3.9%)
Blood transfusion ≥ 2 units	156 (1.6%)	280 (2.8%)
Modified TIMI Severe Hemorrhage[2]	148 (1.5%)	260 (2.6%)
Minor Bleeding[3]	115 (1.2%)	320 (3.2%)
PCI-related bleed[4]	82 (0.8%)	183 (1.8%)
CABG-related bleed[4]	86 (0.9%)	72 (0.7%)

1 Major bleeding was defined as clinically overt bleeding with at least one of the following criteria: fatal, symptomatic intracranial hemorrhage, retroperitoneal hemorrhage, intraocular hemorrhage leading to significant vision loss, bleeding requiring surgical intervention, decrease in Hb of ≥ 3 g/dL, or blood transfusion ≥ 2 units.

2 Modified TIMI severe hemorrhage was defined as fatal hemorrhage, intracranial hemorrhage, cardiac tamponade, or a clinically significant hemorrhage with a decrease in Hb of > 5 g/dL.

3 Minor bleeding was defined as clinically overt bleeding that was not major and that led to interruption of study drug for at least 24 hours, or transfusion of one unit of blood.

4 The number of patients undergoing PCI was 3,422 for ARIXTRA® and 3,410 for enoxaparin and the number of patients undergoing CABG was 956 for ARIXTRA® and 886 for enoxaparin.

5 Patients randomized to ARIXTRA® received 2.5 mg fondaparinux SC once daily for up to 8 days or discharge.

6 Patients randomized to enoxaparin sodium received 1 mg/kg enoxaparin SC twice daily (once daily if creatinine clearance was between 20 mL/min and 30 mL/min) for 2-8 days or until clinically stable.

Table 7 Incidence of Adjudicated Major Bleeding in OASIS 5 at Day 9 in UA/NSTEMI Patients Treated with ARIXTRA® by Renal Function Status at Baseline

Covariate Endpoint/ Timepoint	Number Events / Number Analyzed		OR/HR[1] (95% CI)	Interaction p-value[4]
	ARIXTRA® [2]	Enoxaparin [3]		
On therapy	183/9943 (1.8%)	388/9928 (3.9%)	0.46 (0.38, 0.55)	0.343
<20 mL/min	1/40 (2.5%)	5/43 (11.6%)	0.19 (0.02, 1.75)	
≥20 - <30 mL/min	4/240 (1.7%)	19/239 (7.9%)	0.20 (0.07, 0.59)	
≥30 - <50 mL/min	47/1649 (2.9%)	104/1715 (6.1%)	0.45 (0.32, 0.65)	
≥50 - <80 mL/min	93/4,257 (2.2%)	185/4,188 (4.4%)	0.48 (0.38, 0.62)	
≥80 mL/min	38/3,757 (1.0%)	75/3,743 (2.0%)	0.50 (0.34, 0.74)	
Creatinine clearance not recorded	0/36	1/41 (2.4%)		
Day 9	209/9979 (2.1%)	405/9969 (4.1%)	0.51 (0.43, 0.60)	0.248
<20 mL/min	2/40 (5.0%)	5/43 (11.6%)	0.41 (0.08, 2.11)	
≥20 - <30 mL/min	4/240 (1.7%)	21/239 (8.8%)	0.19 (0.06, 0.54)	
≥30 - <50 mL/min	54/1649 (3.3%)	107/1715 (6.2%)	0.52 (0.37, 0.71)	
≥50 - <80 mL/min	103/4257 (2.4%)	193/4188 (4.6%)	0.52 (0.41, 0.66)	
≥80 mL/min	46/3757 (1.2%)	79/3743 (2.1%)	0.58 (0.40, 0.83)	
Creatinine clearance not recorded	0/36	1/41 (2.4%)		

Note: Creatinine clearance was included as a continuous variable in the estimate of the overall hazard/odds ratio and covariate p-value.

1 Odds ratio for the on-therapy analysis; hazard ratio for the Day 9 analysis.

2 Patients randomized to ARIXTRA® received 2.5 mg fondaparinux SC once daily for up to 8 days or discharge.

3 Patients randomized to enoxaparin sodium received 1 mg/kg enoxaparin SC twice daily (once daily if creatinine clearance was between 20 mL/min and 30 mL/min) for 2-8 days or until clinically stable.

4 Treatment by Covariate Interaction (test for homogeneity of treatment effect).

In a study of 3,235 high-risk UA/NSTEMI patients scheduled for angiography and treated with open-label fondaparinux (FUTURA/OASIS 8), the 2,026 patients indicated for PCI were randomized to receive one of two double-blind dose regimens of adjunctive unfractionated heparin (UFH). All enrolled patients received fondaparinux 2.5 mg subcutaneously, once daily for up to 8 days, or until hospital discharge. Randomized patients received either "low dose" UFH regimen (50 U/kg irrespective of planned GPIIb/IIIa use; non ACT-guided) or "standard dose" UFH regimen (85 U/kg, ACT-guided, if no GPIIb/IIIa use; or 60 U/kg, ACT-guided, if planned GPIIb/IIIa use), immediately prior to the start of the PCI.

The primary endpoint was a composite of peri-PCI (defined as time of randomization up to 48 hours post-PCI) adjudicated major or minor bleeding, or non-adjudicated major vascular access site complications. It is noteworthy that FUTURA/OASIS 8 was underpowered to conclusively rule out any statistically significant differences between both UFH groups.

Table 8 Incidence of Peri-PCI Major or Minor Bleeding, or Major Vascular Access Site Complications, in High-Risk UA/NSTEMI Patients in FUTURA/OASIS 8 Receiving ARIXTRA® With Either Low-Dose or Standard Dose[5] Adjunctive UFH during PCI

Endpoints, n (%)	Incidence		Odds Ratio[1] (95%CI)	p-value
	Low-Dose UFH N = 1,024	Standard Dose UFH N = 1,002		
Primary				
Peri-PCI major [2]or minor[3] bleeding, or major vascular access site complications[4]	48 (4.7%)	58 (5.8%)	0.80 (0.54, 1.19)	0.267
Secondary				
Peri-PCI major bleeding	14 (1.4%)	12 (1.2%)	1.14 (0.53, 2.49)	0.734
Peri-PCI minor bleeding	7 (0.7%)	17 (1.7%)	0.40 (0.16, 0.97)	0.042
Major vascular access site complications	33 (3.2%)	43 (4.3%)	0.74 (0.47, 1.18)	0.207
Peri-PCI major bleeding, or death, MI or TVR up to Day 30.	59 (5.8%)	39 (3.9%)	1.51 (1.00, 2.28)	0.051
Death, MI or TVR up to Day 30.	46 (4.5%)	29 (2.9%)	1.58 (0.98, 2.53)	0.059
Death up to Day 30	8 (0.8%)	6 (0.6%)	1.31 (0.45, 3.78)	0.621
MI up to Day 30	31 (3.0%)	25 (2.5%)	1.22 (0.72, 2.08)	0.466
TVR up to Day 30	9 (0.9%)	3 (0.3%)	2.95 (0.80, 10.93)	0.105

TVR, Target Vessel Revascularisation; MI, Myocardial Infarction

[1] Odds ratio: Low Dose/Standard Dose

[2] Major bleeding was defined as clinically overt bleeding with at least one of the following criteria: fatal, symptomatic intracranial hemorrhage, retroperitoneal hemorrhage, intraocular hemorrhage leading to significant vision loss, bleeding requiring surgical intervention, decrease in Hb of ≥ 3 g/dL, or blood transfusion ≥ 2 units. Peri-PCI includes the time of randomization up to 48 hours post-PCI.

[3] Minor bleeding was defined as clinically overt bleeding that was not major and that led to interruption of study drug for at least 24 hours, or transfusion of one unit of blood.

[4] Major vascular access site complications include large hematoma, pseudoaneurysm requiring treatment, arteriovenous fistula, or other vascular procedures related to the access site.

[5] For description of low-dose or standard dose, see narrative text, two paragraphs above this Table

Risk of catheter thrombosis during PCI

Clinical trials have shown an increased risk of guiding catheter thrombosis in patients treated solely with ARIXTRA® for anticoagulation during percutaneous coronary intervention (PCI) compared to control (see WARNINGS AND PRECAUTIONS, Cardiovascular). The incidence of catheter thrombosis in UA/NSTEMI patients undergoing PCI in OASIS 5 were 0.9% (29/3173) with ARIXTRA®, 0.3% (6/1,883) with enoxaparin alone, and 0.2% (2/1,286) with enoxaparin with adjunctive UFH. In OASIS 5, patients randomized to ARIXTRA® received ARIXTRA® as the sole adjunctive therapy during PCI whereas enoxaparin subjects received enoxaparin with or without UFH during PCI based on the timing since the last subcutaneous injection of enoxaparin.

In ARIXTRA®-treated high risk UA/NSTEMI patients randomized to receive low-dose or standard regimens of UFH during non-primary PCI (see FUTURA/OASIS 8 trial description above), the incidences of adjudicated catheter thrombus were 0.5% (5/1,024), and 0.1%

(1/1,002), respectively (see WARNINGS AND PRECAUTIONS, Cardiovascular). In addition, in non-randomized patients, four (0.3%) cases of confirmed catheter thrombus occurred during diagnostic angiography. Of the 3,235 patients enrolled in the trial, thirteen (0.40%) in total experienced thrombus in the arterial sheath, with 7 cases of sheath thrombosis during angiography and 6 during PCI.

ARIXTRA® should not be used as the sole anticoagulant during PCI because of an increased risk of guiding catheter thrombosis. **An effective anti-thrombin regimen such as unfractionated heparin (UFH) should be administered as an adjunct to PCI according to standard practice (see WARNINGS AND PRECAUTIONS, Cardiovascular).**

Geriatrics: Nearly 8,000 UA/NSTEMI patients, 65 years or older, received treatment with ARIXTRA® in OASIS 5 and FUTURA/OASIS 8. In the OASIS-5 study, the rate of major bleeding at Day 9 was: 1.3% (50/3,885) in patients < 65 years, 2.4% (89/3,644) in those 65-74 years, and 2.9% (71/2,450) in those ≥ 75 years.

Management of STEMI

The rates of major bleeding events reported during the management of STEMI clinical trials with ARIXTRA® 2.5 mg injection are provided in Table 9 below.

Table 9 Bleeding Episodes[1,2] in OASIS 6, Randomized, Controlled Study in STEMI[3]

	Up to 9 days after presenting with STEMI (Number (%) Subjects)					
	Overall		**Stratum 1**		**Stratum 2**	
Investigator reported bleeding events	**ARIXTRA® [3]** N = 5954	**Control (UFH/placebo)** N = 5947	**ARIXTRA® [3]** N = 2808	**Placebo** N=2818	**ARIXTRA® [3]** N = 3146	**UFH** N=3129
Modified TIMI Severe Hemorrhage[1]	78 (1.3%)	94 (1.6%)	34 (1.2%)	48 (1.7%)	44 (1.4%)	46 (1.5%)
Fatal	35 (0.6%)	48 (0.8%)	19 (0.7%)	32 (1.1%)	16 (0.5%)	16 (0.5%)
Intracranial	12 (0.2%)	12 (0.2%)	6 (0.2%)	7 (0.2%)	6 (0.2%)	5 (0.2%)
Cardiac tamponade	26 (0.4%)	47 (0.8%)	15 (0.5%)	30 (1.1%)	11 (0.3%)	17 (0.5%)
Drop in Hgb ≥ 5 g/dL	37 (0.6%)	34 (0.6%)	12 (0.4%)	10 (0.4%)	25 (0.8%)	24 (0.8%)
By Reperfusion strategy						
No reperfusion	13/1415 (0.9%)	20/1367 (1.5%)	3/620 (0.5%)	5/599 (0.8%)	10/795 (1.3%)	15/768 (2.0%)
Thrombolytic group	34/2676 (1.3%)	55/2711 (2.0%)	25/2182 (1.1%)	41/2214 (1.9%)	9/494 (1.8%)	14/497 (2.8%)
Primary PCI	17/1863 (0.9%)	8/1869 (0.4%)	0/6	0/5	17/1857 (0.9%)	8/1864 (0.4%)
Major Bleeding[2]	104 (1.7%)	131 (2.2%)	40 (1.4%)	61 (2.2%)	64 (2.0%)	70 (2.2%)
Minor Bleeding	37 (0.6%)	23 (0.4%)	19 (0.7%)	6 (0.2%)	18 (0.6%)	17 (0.5%)
PCI related bleeding	45 (0.8%)	47 (0.8%)	7 (0.2%)	3 (0.1%)	38 (1.2%)	44 (1.4%)
CABG related bleeding	3 (<0.1%)	6 (0.1%)	1 (<0.1%)	3 (0.1%)	2 (<0.1%)	3 (<0.1%)

[1] Severe hemorrhage was defined according to a modified TIMI criteria as: fatal hemorrhage, intracranial hemorrhage, cardiac tamponade, or a clinically significant hemorrhage with a decrease in Hb of >5 g/dL.

[2] Major bleeding was defined as clinically overt bleeding with at least one of the following criteria: fatal, symptomatic intracranial hemorrhage, retroperitoneal hemorrhage, intraocular hemorrhage leading to significant vision loss, bleeding requiring surgical intervention, decrease in Hb of >3.0 g/dL, or blood transfusion ≥2 units.

[3] Patients randomized to ARIXTRA® received an IV bolus injection of 2.5 mg followed by 2.5 mg by SC injection daily for up to 8 days or discharge.

In those patients who underwent non-primary PCI < 6 hours after the last dose of fondaparinux, the median dose of UFH used was 5000 IU and the incidence of major bleeding was 4.1% (2/49). In those patients who underwent non-primary PCI 6-24 hours after the last dose of fondaparinux, the median dose of UFH was 8000 IU and the incidence of major bleeding was 2% (2/98).

The relative effects of ARIXTRA® compared to control on severe hemorrhage or any hemorrhage up to Day 9 by clopidogrel use were consistent with that observed for the overall population.

Risk of catheter thrombosis during PCI
Clinical trials have shown an increased risk of guiding catheter thrombosis in patients treated solely with ARIXTRA® for anticoagulation during percutaneous coronary intervention (PCI) compared to control (see WARNINGS AND PRECAUTIONS, Cardiovascular). The incidence of catheter thrombus in STEMI patients undergoing primary PCI were 1.18% (22/1,862) for ARIXTRA®, when ARIXTRA® was used as the sole adjunctive therapy, compared to 0% for UFH (0/1,853). In STEMI patients treated with ARIXTRA® undergoing non-primary PCI (234 patients, 238 procedures) who received UFH as an adjunct to the procedure, no cases of guiding catheter thrombus occurred.

In STEMI patients undergoing primary percutaneous coronary intervention (PCI) for reperfusion, the use of ARIXTRA® prior to and during PCI is not recommended (see WARNINGS AND PRECAUTIONS, Cardiovascular, and DOSAGE AND ADMINISTRATION).

Geriatrics: Over 2,300 STEMI patients, 65 years or older, received treatment with ARIXTRA® in OASIS 6. In the STEMI clinical trials with patients receiving ARIXTRA®, the risk of severe hemhorrage was: 0.6% (22/3,565) in patients < 65 years, 1.5% (23/1,518) in those 65-74 years, and 2.2% (19/871) in those ≥ 75 years.

Non-hemorrhagic adverse events
Other adverse events that occurred during treatment with ARIXTRA® or enoxaparin sodium in clinical trials with patients undergoing hip fracture surgery, hip replacement surgery, or knee replacement surgery and that occurred at a rate of at least 2% in either treatment group, are provided in Table 10 and

Table 11 below.

Other adverse events that occurred during treatment with ARIXTRA® or dalteparin sodium in a clinical trial with patients undergoing abdominal surgery that occurred at a rate of at least 2% in either treatment group are provided in Table 12 below.

Table 10 Adverse Events Occurring in Greater Than or Equal to 2 Percent of ARIXTRA® or Enoxaparin Sodium Treated Patients Regardless of Relationship to Study Drug Across Hip Fracture, Hip Replacement Surgery, or Knee Replacement Surgery Studies

Adverse Events	ARIXTRA® 2.5 mg SC once daily N = 3616	Comparator: Low Molecular Weight Heparin or Enoxaparin Sodium[1] N = 3956
Anemia	19.6%	16.9%
Fever	13.6%	15.4%
Nausea	11.3%	12.2%
Edema	8.7%	8.8%
Constipation	8.5%	10.5%
Rash	7.5%	8.3%
Vomiting	5.9%	6.0%
Insomnia	5.0%	5.4%
Wound drainage increased	4.5%	4.7%
Hypokalemia	4.2%	4.1%
Urinary tract infection	3.8%	3.4%
Dizziness	3.6%	4.2%
Purpura	3.5%	3.5%
Hypotension	3.5%	3.2%
Confusion	3.1%	3.3%
Bullous eruption	3.1%	2.6%
Urinary retention	2.9%	3.0%
Hematoma	2.8%	2.8%
Diarrhea	2.5%	2.6%
Dyspepsia	2.4%	2.6%
Post-operative hemorrhage	2.4%	1.7%
Headache	2.0%	2.5%
Pain	1.7%	2.6%

[1] Enoxaparin Sodium dosing regimen: 30 mg every 12 hours or 40 mg once daily.

Table 11 Adverse Events Occurring in Greater Than or Equal to 2 Percent of ARIXTRA® or Placebo Treated Patients Regardless of Relationship to Study Drug During Pre-randomization Open Label Period and Extended Prophylaxis period After Hip Fracture Surgery

	Pre-randomization Open-Label Period (Day 1 to Day 7 ± 1 post-surgery)	**Randomized Double-Blind Extended Prophylaxis Period (Day 8 to Day 28 ± 2 post-surgery)**	
Adverse Events	**ARIXTRA® N = 737**	**ARIXTRA® N =327**	**Placebo SC N = 329**
Constipation	7.1%	1.8%	2.1%
Anemia	5.8%	1.5%	1.2%
Nausea	4.6%	0.3%	1.2%
Confusion	4.1%	1.2%	0.3%
Fever	4.1%	0.3%	1.2%
Urinary tract infection	3.1%	4.0%	4.0%
Vomiting	2.7%	0.6%	1.2%
Post-operative hemorrhage	2.4%	0.6%	0.6%
Hematoma	1.2%	2.1%	0.3%
Surgical site reaction	0.7%	1.5%	2.4%
Diarrhea	0.5%	1.8%	2.4%

Table 12 Adverse Events Occurring in Greater Than or Equal to 2 Percent of Patients Treated With ARIXTRA® or Dalteparin Sodium Undergoing Abdominal Surgery Regardless of Relationship to Study Drug

Adverse Events	**ARIXTRA® 2.5 mg SC once daily** N = 1433	**Dalteparin Sodium 5000 IU SC once daily** N = 1425
Post-operative wound infection	4.9%	4.8%
Post-operative haemorrhage	4.3%	2.9%
Fever	3.7%	3.8%
Surgical site reaction	3.2%	2.8%
Anaemia	2.4%	1.8%
Hypertension	2.4%	2.9%
PNEUMONIA	2.3%	1.6%
VOMITING	2.2%	1.8%

Other adverse events that occurred during treatment with ARIXTRA®, enoxaparin sodium or heparin in the DVT and PE treatment clinical trials and that occurred at a rate of at least 2% in any treatment group are provided in Table 13 below.

Table 13 Adverse Events Occurring in Greater Than or Equal to 2 Percent of ARIXTRA® or Enoxaparin Sodium or Heparin Treated Patients Regardless of Relationship to Study Drug Across VTE Treatment Studies

Adverse Events	ARIXTRA® Treatment Regimen	Enoxaparin Sodium 1 mg/kg SC q 12h	Heparin IV aPTT adjusted
	N = 2294	N = 1101	N = 1092
Constipation	106 (4.6%)	32 (2.9%)	93 (8.5%)
Headache	104 (4.5%)	37 (3.4%)	65 (6.0%)
Insomnia	86 (3.7%)	19 (1.7%)	75 (6.9%)
Fever	81 (3.5%)	32 (2.9%)	47 (4.3%)
Nausea	76 (3.3%)	29 (2.6%)	53 (4.9%)
Urinary Tract Infection	53 (2.3%)	20 (1.8%)	24 (2.2%)
Coughing	48 (2.1%)	7 (0.6%)	26 (2.4%)
Diarrhea	43 (1.9%)	22 (2.0%)	27 (2.5%)
Abdominal Pain	33 (1.4%)	14 (1.3%)	28 (2.6%)
Chest Pain	33 (1.4%)	8 (0.7%)	26 (2.4%)
Leg Pain	31 (1.4%)	10 (0.9%)	22 (2.0%)
Back Pain	30 (1.3%)	11 (1.0%)	34 (3.1%)
Epistaxis	30 (1.3%)	12 (1.1%)	41 (3.8%)
Prothrombin decreased	30 (1.3%)	3 (0.3%)	34 (3.1%)
Anemia	28 (1.2%)	3 (0.3%)	23 (2.1%)
Vomiting	26 (1.1%)	14 (1.3%)	27 (2.5%)
Hypokalemia	25 (1.1%)	2 (0.2%)	23 (2.1%)
Bruise	24 (1.0%)	24 (2.2%)	14 (1.3%)
Anxiety	18 (0.8%)	8 (0.7%)	22 (2.0%)
Hepatic Function abnormal	10 (0.4%)	14 (1.3%)	24 (2.2%)
Hepatic Enzymes increased	7 (0.3%)	52 (4.7%)	30 (2.7%)
ALT increased	7 (0.3%)	47 (4.3%)	8 (0.7%)
AST increased	4 (0.2%)	31 (2.8%)	3 (0.3%)

Other adverse events that occurred during treatment with ARIXTRA®, enoxaparin, UFH or placebo in clinical trials with acute coronary syndrome patients and that occurred at a rate of at least 2% in any treatment group, are described in Table 14 below.

Table 14 Adverse Events Occurring in ≥ 2 % of ARIXTRA® or Control[1] Treated Patients Regardless of Relationship to Study Drug Across Studies of UA/NSTEMI (OASIS 5) and STEMI (OASIS 6)

	Number (%) Subjects							
	OASIS 5		OASIS 6					
			Overall		Stratum 1		Stratum 2	
	ARIXTRA® N=9979	Enoxaparin N=9969	ARIXTRA® N=5954	Control[1] N=5947	ARIXTRA® N=2808	Placebo N=2818	ARIXTRA® N=3146	UFH N=3129
Any AE[2]	2426 (24)	2785 (28)	1933 (32)	1959 (33)	922 (33)	954 (34)	1011 (32)	1005 (32)
Headache	227 (2)	226 (2)	105 (2)	118 (2)	60 (2)	63 (2)	45 (1)	55 (2)
Atrial fibrillation	103 (1)	124 (1)	164 (3)	126 (2)	69 (2)	57 (2)	95 (3)	69 (2)
Pyrexia	96 (<1)	110 (1)	189 (3)	200 (3)	119 (4)	125 (4)	70 (2)	75 (2)
Chest pain	148 (1)	147 (1)	108 (2)	79 (1)	50 (2)	42 (1)	58 (2)	37 (1)
Vomiting	50 (<1)	62 (<1)	74 (1)	74 (1)	47 (2)	42 (1)	27 (1)	32 (1)
Ventricular tachycardia	35 (<1)	28 (<1)	76 (1)	81 (1)	26 (<1)	29 (1)	50 (2)	52 (2)

[1] OASIS 5 is a study in UA/NSTEMI and OASIS 6 is a study in STEMI. Control for the OASIS 5 study was enoxaparin and for the OASIS 6 study was placebo or UFH.

[2] Includes any efficacy outcomes (except hemorrhagic stroke), non-fatal cardiac arrest and heart failure reported as AEs by the investigator in contravention of the protocol.

Other adverse events reported in greater than or equal to 1% of high-risk UA/NSTEMI patients treated with ARIXTRA® and receiving either "low-dose" or "standard dose" of adjunctive intravenous UFH during non-primary PCI in FUTURA/OASIS 8, included headache, pyrexia, post-procedural discharge, hypotension, cough and dizziness. No individual AE occurred in greater than 3% of subjects. For those high-risk UA/NSTEMI patients in the same trial, who were not indicated for PCI and were treated with ARIXTRA® only, the other adverse events occurring in greater than or equal to 1% of patients, included headache (1.5%), gastritis (1.2%), urinary tract infection (1.2%), asthenia (1.1%) and pyrexia (1.1%).

Thrombocytopenia: See WARNINGS AND PRECAUTIONS, Hematologic, *Thrombocytopenia*.

Liver Function Tests

Prophylaxis of VTE following orthopedic surgery

Transient elevation of liver transaminases (AST and ALT) to > 3 times the upper limit of laboratory range have been observed with the peri-operative prophylactic use of ARIXTRA® as have been seen with other antithrombotics such as low molecular weight heparins. Such elevations are fully reversible and are rarely associated with increases in bilirubin. Transient transaminase increases > 3 times upper limit of laboratory range during the extended prophylaxis clinical trial were as follows: ALT - 4 /272 (1.5%) ARIXTRA® vs. 2 /274 (0.7%) placebo; AST - 2 /268 (0.7%) ARIXTRA® vs. 1/ 271 (0.4%) placebo. However, these increases were reversible and there was no significant difference in the change in the hepatic enzymes between the two treatment groups from the baseline post-randomization period to the last value on double

blind treatment.

Treatment of DVT and PE
In the DVT and PE treatment clinical trials asymptomatic increases in AST and ALT levels > 3 times the upper limit of normal of the laboratory reference range have been reported in 0.7% and 1.3% of patients, respectively, during the ARIXTRA® injection treatment regimen.

In comparison, these increases have been reported in 4.8% and 12.3% of patients, respectively, in the DVT treatment trial during treatment with enoxaparin sodium 1 mg/kg every 12 hours, and in 2.9% and 8.7% of patients, respectively, in the PE treatment trial during treatment with aPTT adjusted heparin.

Allergic Reaction
Skin rash and allergic reactions have been observed with ARIXTRA use, but are uncommon. As with any subcutaneous injection, mild local irritation (injection site bleeding, rash and pruritis) may occur following subcutaneous injection of ARIXTRA®.
Very rare reports of angioedema and anaphylactoid/anaphylactic reactions (< 0.01%) have been received.

Other Adverse Reactions
Other adverse reactions that occurred during treatment with ARIXTRA® in clinical trials with patients undergoing hip fracture surgery, hip replacement surgery, knee replacement surgery or abdominal surgery and that occurred at a rate of less than 1.0%, include the following: thrombocytopenia, thrombocythemia, abnormal platelets, and coagulation disorder. Adverse reactions events that have occurred at a rate of less than 0.1% in patients during clinical trials include: somnolence, vertigo, dyspnea, fatigue, flushing, and syncope.

7.2 Post-Market Adverse Reactions

The following adverse reactions have been identified during post-approval use of ARIXTRA®.

Rare spontaneous reports of elevated aPTT have been received at the 2.5 mg dose. A causal association between treatment with fondaparinux and the occurrence of elevated aPTT has not been established.

8 DRUG INTERACTIONS

8.1 Drug-Drug Interactions

In clinical studies performed with ARIXTRA® (fondaparinux sodium), the concomitant use of oral anticoagulants (warfarin), platelet inhibitors (acetylsalicylic acid), NSAIDs (piroxicam) and digoxin did not interact with the pharmacokinetics/pharmacodynamics of ARIXTRA®. In addition, ARIXTRA® neither influenced the pharmacodynamics of warfarin, acetylsalicylic acid, piroxicam and digoxin, nor the pharmacokinetics of digoxin at steady state.

Agents that may enhance the risk of hemorrhage should be discontinued prior to initiation of ARIXTRA® therapy unless indicated for the management of the underlying condition, such as vitamin K antagonists for the treatment of venous thromboembolism (VTE). If co-administration is necessary, close monitoring may be appropriate.

Since fondaparinux does not inhibit isozymes of the CYP P450 system *in vitro* (CYP 1A2, CYP 2A6, CYP 2C9, CYP 2C19, CYP 2D6, CYP 2E1 or CYP 3A4), ARIXTRA® is not expected to interact with other drugs metabolized *in vivo* via these isozymes.

ARIXTRA® does not bind significantly to plasma proteins other than ATIII, therefore, drug interactions by protein binding displacement are not expected.

8.2 Drug-Food Interactions

Interactions with food have not been established.

8.3 Drug-Herb Interactions

Interactions with herbal products have not been established.

8.4 Drug-Laboratory Test Interactions

See WARNINGS AND PRECAUTIONS - Monitoring, Laboratory and Coagulation Tests.

9 ACTION AND CLINICAL PHARMACOLOGY

9.1 Mechanism of Action

ARIXTRA® (fondaparinux sodium) Injection is a synthetic and specific inhibitor of activated Factor X (Xa). As ARIXTRA® has no animal-sourced components, there is no risk of animal contamination such as transmissable spongiform encephalitis (TSE).

The mechanism of action of ARIXTRA® is the potentiation of antithrombin III (ATIII) which selectively inhibits Factor Xa. By selectively binding to ATIII, ARIXTRA® potentiates approximately 300 times the neutralization of Factor Xa. Neutralization of Factor Xa interrupts the blood coagulation cascade and thus inhibits thrombin formation and thrombus development.

ARIXTRA® does not inactivate thrombin (activated Factor II) and has no effect on platelets. At the recommended dose, ARIXTRA® does not affect fibrinolytic activity or bleeding time.

At equivalent antithrombotic concentrations, experimental bleeding models demonstrate that ARIXTRA® induces less bleeding than unfractionated heparin.

ARIXTRA® does not bind to Human Platelet Factor 4 (unlike heparin) and does not cross-react with sera from patients with heparin-induced thrombocytopenia. No thrombocytopenia with suspected immuno-allergic pathophysiology was documented in the overall clinical development program or in post-marketing experience.

Anti-Xa Activity: The pharmacodynamics/pharmacokinetics of fondaparinux sodium are derived from fondaparinux plasma concentrations quantified via anti-Factor Xa activity. Only fondaparinux can be used to calibrate the anti-Xa assay. (The international standards of heparin or Low Molecular Weight Heparin [LMWH] are not appropriate for this use). As a result, the activity of fondaparinux sodium is expressed as milligram (mg) of the fondaparinux calibrator. The anti-Xa activity of the drug increases with increasing drug concentration, reaching maximum values in approximately 3 hours.

9.2 Pharmacodynamics

Effect on thrombosis in animal models

Fondaparinux has dose-dependent antithrombotic activity in a variety of models of experimental thrombosis.

The inhibitory activity varies according to the nature of the thrombotic stimulus and the location of the thrombus i.e. venous (low shear) and arterial (high shear).

Antithrombotic activity is generally achieved at concentrations below those required to saturate plasma ATIII concentrations, with the exception of the inhibition of the thromboplastin-induced thromboembolism which occurs at doses far above antithrombin III-saturating levels. The duration of the antithrombotic activity is correlated with that of anti-factor Xa activity.

Safety Pharmacology

Fondaparinux sodium:

- Showed no relevant effects on the central nervous system
- Did not affect body weight, body temperature and gastro-intestinal motility
- Had no significant effect on electrolyte balance
- Did not induce relevant changes in cardiovascular and respiration parameters
- Did not affect coagulation time, defined as aPTT and PT (see WARNINGS AND PRECAUTIONS, Monitoring, Laboratory and Coagulation Tests), blood cell counts, hemoglobin concentration and hematocrit in animals
- Had little effect on bleeding in the subdermal bleeding model in the rat and in the ear bleeding model in the rabbit at doses that are 25 times higher than the dose resulting in the saturation of antithrombin III (0.8 mg/kg)
- Did not bind to Human Platelet Factor 4 (unlike heparin) and did not cross-react with Heparin Induced Thrombocytopenic (HIT) sera from HIT-patients.
- Did not influence lipid metabolism through the release of triglyceride lipase activity in rats (unlike heparin)

9.3 Pharmacokinetics

Absorption: Following a single 4 mg i.v. bolus administration to normal healthy subjects, mean peak fondaparinux plasma concentration is approximately 0.81 mg/L at the first sampling time point of 5 minutes. After subcutaneous dosing, fondaparinux is completely and rapidly absorbed, with an absolute bioavailability of 100%. Following a single subcutaneous injection of 2.5 mg, peak plasma concentration (C_{max} = 0.34 mg/L) is obtained 2 hours post-dosing. Plasma concentrations of half the mean C_{max} values are reached 25 minutes post-dosing.

Pharmacokinetics of fondaparinux are linear in the range of 2 to 8 mg by the subcutaneous route. At steady state, mean plasma concentrations 2 hours post dosing ranged between 0.32 and 0.47 mg/L in patients undergoing orthopedic surgeries receiving ARIXTRA® 2.5 mg.

In patients with symptomatic deep vein thrombosis and pulmonary embolism undergoing treatment with fondaparinux sodium injection 5 mg (body weight < 50 kg), 7.5 mg (body weight 50-100 kg) and 10 mg (body weight > 100 kg) once daily, the body-weight-adjusted doses provide similar exposure across all body weight categories. The peak steady-state plasma concentration is, on average, 1.20-1.26 mg/L. In these patients, the minimum steady-state plasma concentration is 0.46-0.62 mg/L.

Distribution: In healthy adults, intravenously or subcutaneously administered fondaparinux distributes mainly in blood as evidenced by steady state and non-steady state apparent volume of distribution of 7 to 11 L.

In vitro fondaparinux is highly (at least 94% in the concentration range from 0.5 to 2 mg/L) and specifically bound to ATIII and does not bind significantly to other plasma proteins, including Platelet Factor 4 (PF4).

Metabolism: There is no evidence that fondaparinux is metabolized since most of the administered dose is eliminated unchanged in urine.

Elimination: The elimination half life ($T_{1/2}$) is 17 to 21 hours in healthy subjects.

Up to 77% of a single subcutaneous dose of fondaparinux is excreted in urine as unchanged compound in 72 hours in healthy individuals up to 75 years of age.

Special Populations and Conditions

Pediatrics: The pharmacokinetics of fondaparinux have not been investigated in pediatric patients.

Geriatrics: Fondaparinux elimination is prolonged in patients over 75 years old. In studies evaluating fondaparinux sodium 2.5 mg prophylaxis in hip fracture surgery or elective hip surgery, the total clearance of fondaparinux was approximately 25% lower in patients over 75 years old as compared to patients less than 65 years old. A similar pattern is observed in DVT and PE treatment patients.

Following a single intravenous dose of fondaparinux 4 mg in healthy elderly subjects, a mean C_{max} of 0.86 mg/L was observed at the first sampling timepoint of 5 minutes. Other pharmacokinetic parameters following intravenous administration were similar to those observed for subcutaneous administration.

Hepatic Insufficiency: Unbound concentrations of fondaparinux are expected to be unchanged in patients with mild to moderate hepatic insufficiency, and therefore, no dose adjustment is necessary based on pharmacokinetics. Following a single, subcutaneous dose of fondaparinux in subjects with moderate hepatic insufficiency (Child-Pugh Category B), C_{max} and AUC were decreased by 22% and 39%, respectively, as compared to subjects with normal liver function. The lower plasma concentrations of fondaparinux were attributed to reduced binding to ATIII secondary to the lower ATIII plasma concentrations in subjects with hepatic insufficiency thereby resulting in increased renal clearance of fondaparinux. There were no clinically relevant differences in the pharmacodynamic measures as assessed by aPTT, PT and ATIII concentrations, indicating that the effect of fondaparinux in subjects with hepatic impairment was similar to that in individuals with normal liver function.

The pharmacokinetics of fondaparinux have not been studied in patients with severe hepatic insufficiency (see DOSAGE AND ADMINISTRATION, Use in Patients with Hepatic Insufficiency and WARNINGS AND PRECAUTIONS).

Renal Insufficiency: Fondaparinux elimination is prolonged in patients with renal insufficiency since the major route of elimination is urinary excretion of unchanged drug. In patients undergoing prophylaxis following elective hip surgery or hip fracture surgery, the total clearance of fondaparinux is approximately 25% lower in patients with mild renal insufficiency (creatinine clearance 50 to 80 mL/min), approximately 40% lower in patients with moderate renal insufficiency (creatinine clearance 30 to 50 mL/min) and approximately 55% lower in patients with severe renal insufficiency (< 30 mL/min) compared to patients with normal renal function. The associated terminal half-life values were 29 hours in moderate and 72 hours in patients with severe renal insufficiency. A similar pattern is observed in DVT and PE treatment patients (see WARNINGS AND PRECAUTIONS, Renal).

Patients Weighing Less Than 50 kg: Total clearance of fondaparinux sodium is decreased by approximately 30% in patients weighing less than 50 kg (see WARNINGS AND PRECAUTIONS, Low Body Weight, and DOSAGE AND ADMINISTRATION, Use in Patients with Low Body Weight).

10 STORAGE, STABILITY AND DISPOSAL

ARIXTRA® (fondaparinux sodium) injection should be stored below 25°C. Do not freeze.

If ARIXTRA® is added to a 0.9% saline minibag it should be infused immediately, but can be stored between 15-30°C for up to 24 hours. Minibags are typically composed of a variety of polymers including PVC, polyethylene, polypropylene, or styrene-ethylene-butadiene, individually or in combination.

11 SPECIAL HANDLING INSTRUCTIONS

ARIXTRA® pre-filled syringes come with a built-in automatic needle protection system to prevent needle stick injuries following injection.

Keep out of reach of children. Single dose syringes. Discard unused portion.

PART II: SCIENTIFIC INFORMATION

12 PHARMACEUTICAL INFORMATION

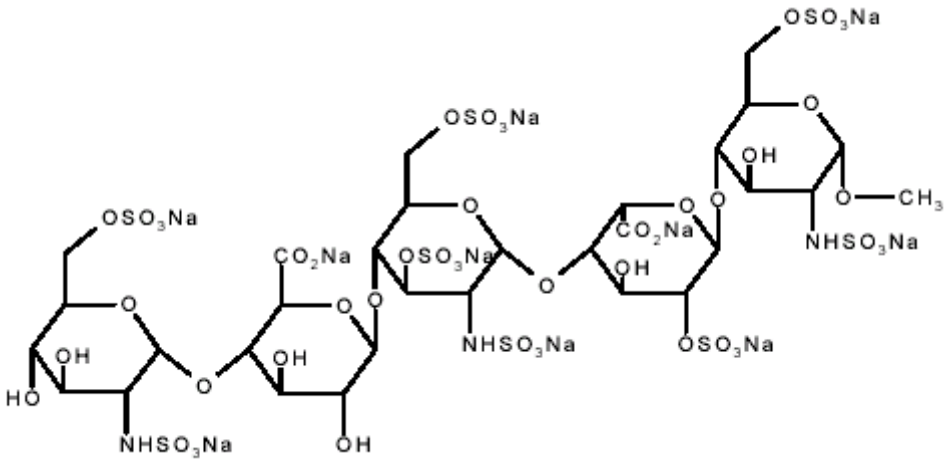
Drug Substance

Proper name: fondaparinux sodium

Chemical name: methyl O-2-deoxy-6-O-sulfo-2-(sulfoamino)-α-D-glucopyranosyl-(1→ 4)-O-β-D-glucopyranuronosyl-(1→4)-O-2-deoxy-3,6-di-O-sulfo-2-(sulfoamino) -α-D-glucopyranosyl-(1 →4)-O-2-O-sulfo-α-L-idopyranuronosyl-(1→4)-2-deoxy-6-O-sulfo-2-(sulfoamino)- α-D-glucopyranoside, decasodium salt

Molecular formula and molecular mass: $C_{31}H_{43}N_3Na_{10}O_{49}S_8$

Structural formula:



Molecular weight: 1728

Physicochemical properties: pH is 7.1 at a concentration of 2.5% (m/V)

Solubility: Freely soluble at any pH (>2 g in 1 mL water), sodium chloride solution, and sodium hydroxide solution. Practically insoluble (less than 1 g in 10,000 mL) in ethanol.

Composition: Each pre-filled syringe of ARIXTRA®, affixed with an automatic needle protection system, contains 2.5 mg of fondaparinux sodium in 0.5 mL, 5.0 mg of fondaparinux sodium in 0.4 mL, 7.5 mg of fondaparinux sodium in 0.6 mL or 10.0 mg of fondaparinux sodium in 0.8 mL of an isotonic solution of sodium chloride, water for injection and if necessary, sodium hydroxide or hydrochloric acid for pH adjustment.

13 CLINICAL TRIALS

Prophylaxis of Thromboembolic Events Following Hip Fracture Surgery

Table 15 Summary of Patient Demographics for Clinical Trials in the Prophylaxis of Thromboembolic Events Following Hip Fracture Surgery

Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
Randomized, double-blind	2.5 mg subcutaneous once daily	1711	77 (17-101)	25% men 75% women

In a randomized, double-blind, clinical trial in patients undergoing hip fracture surgery, ARIXTRA® (fondaparinux sodium) 2.5 mg subcutaneous (SC) once daily was compared to enoxaparin 40 mg SC once daily (the dose of enoxaparin sodium approved for use in prophylaxis in conjunction with orthopedic surgery in Canada is 30 mg SC twice daily).

A total of 1711 patients were randomized and 1673 were treated. Patients ranged in age from 17-101 years (mean age 77 years) with 25% men and 75% women. Patients were 99% Caucasian, 1% other races. Patients with multiple trauma affecting more than one organ system, serum creatinine level more than 180 µmol/L (2 mg/dL), or platelet count less than 100,000/mm^3 were excluded from the trial. ARIXTRA® was initiated 6 hours after surgery in 88% of patients and the comparator was initiated an average of 18 hours after surgery in 74% of patients. For both drugs, treatment was continued for 7 ± 2 days. Efficacy results are provided in Table 16 below. Major bleeding episodes for both drugs are provided in Table 1 and Table 2 (see ADVERSE REACTIONS).

Table 16 Efficacy Results of Study in the Prophylaxis of Thromboembolic Events Following Hip Fracture Surgery

Endpoint	**Associated value and statistical significance for ARIXTRA® 2.5 mg SC once daily[1]**	**Associated value and statistical significance for Enoxaparin 40 mg SC once daily[1]**
All treated Hip Fracture Surgery Patients	**N=831**	**N=840**
All Evaluable[2] Hip Fracture Surgery Patients		
Venous Thromboembolic Event (VTE[3])	52/626 8.3%[4] (6.3, 10.8)[5]	119/624 19.1% (16.1, 22.4)
All Deep Vein Thrombosis (DVT)	49/624 7.9%[4] (5.9, 10.2)	117/623 18.8% (15.8, 22.1)
Proximal DVT	6/650 0.9%[4] (0.3, 2.0)	28/646 4.3% (2.9, 6.2)
Symptomatic Pulmonary Embolism (PE)	3/831 0.4%[6] (0.1, 1.1)	3/840 0.4% (0.1, 1.0)

1 ARIXTRA® was initiated 6 hours after surgery in 88% of patients and the enoxaparin was initiated an average of 18 hours after surgery in 74% of patients.
2 Evaluable patients were those who were treated and underwent the appropriate surgery (i.e. hip fracture surgery of the upper third of the femur), with an adequate efficacy assessment up to Day 11.
3 VTE was a composite of documented DVT and/or documented symptomatic PE reported up to Day 11.
4 p-value <0.001
5 Number in parentheses indicates 95% confidence interval
6 p-value: Not Significant (NS)

Extended Prophylaxis of Thromboembolic Events

Table 17 Summary of Patient Demographics for Clinical Trials in the Extended Prophylaxis of Thromboembolic Events Following Orthopedic Surgery

Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
Randomized	2.5 mg subcutaneous once daily for 7 ± 1 days. At the end of this period, randomized to receive either ARIXTRA® 2.5 mg od or placebo, for 21 ± 2 days.	ARIXTRA®: n=737 open period ARIXTRA®: n=326 Placebo: n=330	75 (23-96)	29% men 71% women

In an unblinded manner, 737 patients undergoing hip fracture surgery were initially treated with ARIXTRA® 2.5 mg once daily for 7 ± 1 days. At the end of this period, 326 patients were randomized to receive ARIXTRA® 2.5 mg once daily and 330 to placebo in a double-blind trial for 21 ± 2 days; 81 patients were not eligible for randomization. Patients ranged in age from 23 to 96 years (mean age 75 years) and were 29% men and 71% women. Patients were 99% Caucasian and 1% other races. Patients undergoing standard surgery for fracture of the upper third of the femur or the femoral head and neck not more than 48 hours after admission were entered unless they had, mainly, active and significant bleeding, bleeding disorders, creatinine level above 180 mol/L (2.0 mg/dL), received other anticoagulants between admission and surgery and diagnosed deep vein thrombus or pulmonary emboli (PE) during screening or pre-randomization period.

The primary efficacy endpoint was the composite of the following adjudicated VTE outcomes, evaluated during the randomization period up to day 24: symptomatic DVT and/or adjudicated non-fatal PE, and mandatory venogram positive for VTE. The efficacy data are provided in Table 18 below and demonstrate that extended prophylaxis with fondaparinux sodium was associated with a VTE rate of 1.4% compared with a VTE rate of 35.0% for placebo for a relative risk reduction of 95.9% (95% CI=[-99.7; -87.2], p<0.0001). Major bleeding episodes for non-randomized and randomized patients are provided in Table 3 (see ADVERSE REACTIONS, Hemorrhage).

Table 18 Efficacy of ARIXTRA® Injection In the Extended Prophylaxis Period (Day 7 ± 1 to Day 28 ± 2) Number and Percentage of Thromboembolic Events in Patients Who had Undergone Hip Fracture Surgery One Week Earlier.[1]

Endpoint	ARIXTRA® 2.5 mg SC once daily	Placebo SC once daily
All Randomized Treated Hip Fracture Surgery Patients	N=326	N=330
All Randomized Evaluable Hip Fracture Surgery Patients[2]		
VTE[3]	3/208 1.4%[4] (0.3, 4.2)[5]	77/220 35.0% (28.7, 41.7)
All DVT	3/208 1.4%[4] (0.3, 4.2)	74/218 33.9% (27.7, 40.6)
Proximal DVT	2/221 0.9%[4] (0.1, 3.2)	35/222 15.8% (11.2, 21.2)
Symptomatic VTE	1/326 0.3%[6] (0.1, 1.7)	9/330 2.7% (1.3, 5.1)

1 During the one week pre-randomization period preceding the Extended Prophylaxis Period all patients had been treated with open-label ARIXTRA® 2.5 mg SC once daily.

2 Evaluable patients were those who were treated in the post-randomization period, with an adequate efficacy assessment up to Day 24 following randomization.

3 VTE was a composite of documented DVT and/or documented symptomatic PE reported up to Day 24 following randomization.

4 p-value <0.001

5 Number in parentheses indicates 95% confidence interval

6 p-value = 0.021

Prophylaxis of Thromboembolic Events following Hip Replacement Surgery

Table 19 Summary of Patient Demographics for Clinical Trials in the Prophylaxis of Thromboembolic Events Following Hip Replacement Surgery

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
1	Randomized, double-blind	2.5 mg fondaparinux subcutaneous once daily vs. 30 mg enoxaparin bid.	2275	65 (18-92)	48% men 52% women
2	Randomized, double-blind	2.5 mg fondaparinux subcutaneous once daily vs. 40 mg enoxaparin once daily	2309	65 (24-97)	42% men 58% women

In two randomized, double-blind, clinical trials in patients undergoing hip replacement surgery, ARIXTRA® 2.5 mg SC once daily was compared to either enoxaparin sodium 30 mg SC every 12 hours (Study 1) or to enoxaparin sodium 40 mg SC once a day (Study 2). The dose of enoxaparin sodium approved for prophylaxis in conjunction with orthopedic surgery in Canada is 30 mg SC twice daily. In Study 1, a total of 2,275 patients were randomized and 2,257 were treated. Patients ranged in age from 18 to 92 years (mean age 65 years) with 48% men and 52% women. Patients were 94% Caucasian, 4% Black, <1% Asian, and 2% others. In Study 2, a total of 2,309 patients were randomized and 2,273 were treated. Patients ranged in age from 24 to 97 years (mean age 65 years) with 42% men and 58% women. Patients were 99% Caucasian, and 1% other races. Patients with serum creatinine level more than 180 µmol/L (2 mg/dL), or platelet count less than 100,000/mm^3 were excluded from both trials.

In Study 1, ARIXTRA® was initiated 6 ± 2 hours (mean 6.5 hrs) after surgery in 92% of patients and enoxaparin sodium was initiated 12 to 24 hours (mean 20.25 hrs) after surgery in 97% of patients. In Study 2, ARIXTRA® was initiated 6 ± 2 hours (mean 6.25 hrs) after surgery in 86% of patients and enoxaparin sodium was initiated 12 hours before surgery in 78% of patients. The first post-operative enoxaparin sodium dose was given before 12 hours after surgery in 60% of patients and 12 to 24 hours after surgery in 35% of patients with a mean of 13 hrs. For both studies, both study treatments were continued for 7 ± 2 days. Efficacy results are provided in Table 20 below. Major bleeding episodes for both drugs are provided in Table 1 and Table 2 (see ADVERSE REACTIONS).

Table 20 Efficacy Results of Study in the Prophylaxis of Thromboembolic Events Following Hip Replacement Surgery

Endpoint	Study 1		Study 2	
	ARIXTRA® 2.5 mg SC once daily[1]	**Enoxaparin 30 mg SC every 12 hr[2]**	**ARIXTRA® 2.5 mg SC once daily[1]**	**Enoxaparin 40 mg SC once daily[3]**
All Treated Hip Replacement Surgery Patients				
	N=1126	N=1128	N=1129	N=1123
All Evaluable[4] Hip Replacement Surgery Patients				
VTE[5]	48/787 6.1%[6] (4.5, 8.0)[7]	66/797 8.3% (6.5, 10.4)	37/908 4.1%[9] (2.9, 5.6)	85/919 9.2% (7.5, 11.3)
All DVT	44/784 5.6%[8] (4.1, 7.5)	65/796 8.2% (6.4, 10.3)	36/908 4.0%[9] (2.8, 5.4)	83/918 9.0% (7.3, 11.1)
Proximal DVT	14/816 1.7%[6] (0.9, 2.9)	10/830 1.2% (0.6, 2.2)	6/922 0.7%[9] (0.2, 1.4)	23/927 2.5% (1.6, 3.7)
Symptomatic PE	5/1126 0.4%[6] (0.1, 1.0)	1/1128 0.1% (0.0, 0.5)	2/1129 0.2%[6] (0.0, 0.6)	2/1123 0.2% (0.0, 0.6)

1 Patients randomized to ARIXTRA® 2.5 mg were to receive the first injection 6 ± 2 hours after surgery providing that hemostasis had been achieved.

2 Patients randomized to enoxaparin sodium were to receive the first injection between 12 and 24 hours after surgery.

3 Patients randomized to enoxaparin sodium were to receive the first injection 12 hours prior to surgery except in the case of spinal anesthesia. The first post-operative enoxaparin sodium dose was to be given between 12 to 24 hours after surgery.

4 Evaluable patients were those who were treated and underwent the appropriate surgery (i.e. elective hip replacement surgery), with an adequate efficacy assessment up to Day 11.

5 VTE was a composite of documented DVT and/or documented symptomatic PE reported up to Day 11.

6 p-value versus enoxaparin sodium: NS

7 Number in parentheses indicates 95% confidence interval

8 p-value versus enoxaparin sodium in study 1: <0.05

9 p-value versus enoxaparin sodium in study 2: <0.01

Prophylaxis of Thromboembolic Events following Knee Replacement Surgery

Table 21 Summary of Patient Demographics for Clinical Trials in the Prophylaxis of Thromboembolic Events Following Knee Replacement Surgery

Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
Randomized, double-blind	2.5 mg fondaparinux subcutaneous once daily vs. 30 mg enoxaparin SC bid.	1049	68 (19-94)	41% men 59% women

In a randomized, double-blind, clinical trial in patients undergoing knee replacement surgery (i.e., surgery requiring resection of the distal end of the femur or proximal end of the tibia), ARIXTRA® 2.5 mg SC once daily was compared to enoxaparin sodium 30 mg SC every 12 hours. A total of 1,049 patients were randomized and 1,034 were treated. Patients ranged in age from 19 to 94 years (mean age 68 years) with 41% men and 59% women. Patients were 88% Caucasian, 8% Black, <1% Asian, and 3% others. Patients with serum creatinine level more than 180 µmol/L (2 mg/dL), or platelet count less than 100,000/mm^3 were excluded from the trial. ARIXTRA® was initiated 6 ± 2 hours (mean 6.25 hrs) after surgery in 94% of patients and enoxaparin sodium was initiated 12 to 24 hours (mean 21 hrs) after surgery in 96% of patients. For both drugs, treatment was continued to 7 ± 2 days. Efficacy results are provided in Table 22 below. Major bleeding episodes for both drugs are provided in Table 1 and Table 2 (see ADVERSE REACTIONS).

Table 22 Efficacy Results of Study in the Prophylaxis of Thromboembolic Events Following Knee Replacement Surgery

Endpoint	ARIXTRA®[1]	Enoxaparin[2]
All treated Knee Replacement Surgery Patients	N=517	N=517
All Evaluable[3] Knee Replacement Surgery Patients		
VTE[4]	45/361 12.5%[5] (9.2, 16.3)[6]	101/363 27.8% (23.3, 32.7)
All DVT	45/361 12.5%[5] (9.2, 16.3)	98/361 27.1% (22.6, 32.0)
Proximal DVT	9/368 2.4%[7] (1.1, 4.6)	20/372 5.4% (3.3, 8.2)
Symptomatic PE	1/517 0.2%[7] (0.0, 1.1)	4/517 0.8% (0.2, 2.0)

1 Patients randomized to ARIXTRA® 2.5 mg received the first injection 6 ± 2 hours after surgery providing that hemostasis had been achieved.
2 Patients randomized to enoxaparin sodium received the first injection at 21 ± 2 hours after surgery closure providing that hemostasis had been achieved.
3 Evaluable patients were those who were treated and underwent the appropriate surgery (i.e. knee replacement surgery), with an adequate efficacy assessment up to Day 11.
4 VTE was a composite of documented DVT and/or documented symptomatic PE reported up to Day 11.
5 p-value <0.001
6 Number in parentheses indicates 95% confidence interval
7 p-value: NS

Prophylaxis of Thromboembolic Events following Abdominal Surgery

In a double-blind, double-dummy clinical trial, 2,927 patients at high risk of thromboembolic complication while undergoing abdominal surgery were randomized to ARIXTRA® 2.5 mg SC once daily started 6 hours postoperatively or dalteparin sodium 5,000 IU SC once daily (2,500 IU SC 2 hours before and a 2,500 IU SC 12 hours after operation on the first day). Both treatments were given for 5 to 9 days to 2,858 patients who were then followed-up for one month. Patients were 17 to 93 years (mean age 65 years), 55% were men and 97% were Caucasian. Patients undergoing urological (other than kidney), gynaecological, vascular, or laparoscopic surgery were excluded.

While it had been originally planned to include any patients at high risk of venous thomboembolic events (VTE) when undergoing abdominal surgery, it was noted during a blinded review of the data that VTE rate was lower than expected. It was then decided to recruit mainly cancer patients as these patients have a higher risk of VTE. Sixty-nine percent (69%) of study patients underwent cancer-related abdominal surgery.

The study was initially designed to show superiority of ARIXTRA® over dalteparin. Assuming a frequency of VTE of 7% with dalteparin, 1,000 evaluable patients per treatment group would give a power greater than 75% to detect a targeted relative risk reduction of 40%. However, it was observed early after the start of the study that the VTE rate was much lower than anticipated and that since this trend continued until the end, it became evident that superiority could not be demonstrated. The Steering Committee decided at the very end, but before database lock-up and un-blinding, to also perform a non-inferiority analysis. The results of two meta-analyses were used to determine the non-inferiority margin. One meta-analysis evaluated the effects of perioperative administration of subcutaneous heparin compared to placebo on VTE and pulmonary embolism. The other and more pertinent meta-analysis used the results of studies comparing the effects of low molecular weight heparins and heparin on VTE in patients undergoing general and cancer surgery. An indirect confidence interval method was used to select a non-inferiority margin of 1.7 (odds ratio) which corresponds to preserving 63% of the minimal effect expected with low molecular weight heparins.

In all evaluable patients (N=2,058), the incidence of total venous thromboembolic events with ARIXTRA® was 4.6% (47/1,027) and with dalteparin was 6.1% (62/1,021) for an absolute risk reduction of 1.5% and odds ratio reduction of 25.8% (95% CI: -9.5%, +49.7%). The difference in total VTE between the two groups was not statistically significant and was mainly due to a reduction in asymptomatic distal deep vein thrombosis (DVT). The incidence of symptomatic DVT was similar between the groups: 6/1,027 (0.4%) in the ARIXTRA® group and 5/1,021 (0.3%) in the dalteparin group. In patients undergoing cancer surgery, 69% of the 2058 evaluable patients, the VTE rate was 4.7% in the ARIXTRA® group and 7.7% in the dalteparin group.

Major bleeding was observed in 3.4% (49/1,433) of the ARIXTRA® treated patients and 2.4% (34/1,425) of the dalteparin-treated patients. For other bleeding events see Table 4 under ADVERSE REACTIONS - Prophylaxis of VTE following abdominal surgery. See also WARNINGS AND PRECAUTIONS - Renal - *Prophylaxis of VTE following orthopedic or abdominal surgery.*

Treatment of Deep Vein Thrombosis and Pulmonary Embolism

The ARIXTRA® clinical program in treatment of venous thromboembolism was designed to demonstrate the efficacy of ARIXTRA® for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE). Over 4,874 patients were studied in controlled Phase II and III clinical studies.

Treatment of Deep Vein Thrombosis

Table 23 Summary of Patient Demographics for Clinical Trial in the Treatment of Deep Vein Thrombosis

Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
Randomized, double-blind	5 mg (body wt < 50 kg) 7.5 mg (body wt 50 - 100 kg) 10 mg (body wt > 100 kg) fondaparinux subcutaneous once daily vs. 1 mg/kg enoxaparin SC every 12 hours	2205	61 (18-95)	53% men 47% women

In a randomized, double-blind, clinical trial in patients with a confirmed diagnosis of acute symptomatic DVT, ARIXTRA® 5 mg (body weight < 50 kg), 7.5 mg (body weight 50-100 kg) or 10 mg (body weight > 100 kg) SC once daily (ARIXTRA® treatment regimen) was compared to enoxaparin sodium 1 mg/kg SC every 12 hours in both hospitalized and non-hospitalized patients. Outpatient and home treatment of ARIXTRA® was permitted, and approximately 32% of patients were discharged home from the hospital while receiving fondaparinux therapy.

A total of 2,205 patients were randomized and 2,192 were treated. Patients ranged in age from 18-95 years (mean age 61 years) with 53% men and 47% women. Patients were 97% Caucasian, 2% Black and 1% other races. For both groups, treatment continued for at least 5 days, and both treatment groups received Vitamin K antagonist therapy initiated within 72 hours after the first study drug administration and continued for 90 ± 7 days, with regular dose adjustments to achieve an INR of 2-3. The primary efficacy endpoint was confirmed, symptomatic, recurrent VTE reported up to Day 97. Treatment with ARIXTRA® was associated with a VTE rate of 3.9% compared with a VTE rate of 4.1% for enoxaparin sodium. The efficacy data are provided in Table 24 below.

Table 24 Efficacy of ARIXTRA® Injection In the Treatment of Deep Vein Thrombosis

Endpoint	ARIXTRA®[1] 5, 7.5 or 10 mg SC once daily (Treatment Regimen)	Enoxaparin Sodium[1] 1 mg/kg SC q 12h
All Randomized DVT Patients	N=1098	N=1107
Total VTE[2]	43[3] (3.9%)	45 (4.1%)
DVT only	18 (1.6%)	28 (2.5%)
Non-fatal PE	20 (1.8%)	12 (1.1%)
Fatal VTE	5 (0.5%)	5 (0.5%)

1 Patients were also treated with vitamin K antagonists initiated within 72 hours after the first study drug administration.
2 VTE was a composite of symptomatic recurrent VTE or fatal VTE reported up to Day 97.
3 The 95% confidence interval for the treatment difference for total VTE was: -1.8% to 1.5%.

Treatment of Pulmonary Embolism

Table 25 Summary of Patient Demographics for Clinical Trial in the Treatment of Pulmonary Embolism

Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
Randomized, open label	5 mg (body wt < 50 kg) 7.5 mg (body wt 50 - 100 kg) 10 mg (body wt > 100 kg) fondaparinux subcutaneous once daily vs. heparin IV bolus (5000 units) followed by aPPT adjusted continuous IV infusion	2213	62 (18-97)	44% men 56% women

In a randomized, open-label, clinical trial in patients with a confirmed diagnosis of acute symptomatic PE, with or without DVT, ARIXTRA® 5 mg (body weight < 50 kg), 7.5 mg (body weight 50-100 kg) or 10 mg (body weight > 100 kg) SC once daily (ARIXTRA® treatment regimen) was compared to heparin IV bolus (5,000 units) followed by a continuous IV infusion adjusted to maintain 1.5-2.5 times aPTT control value. Outpatient and home treatment of ARIXTRA® was permitted, and approximately 15% of patients were discharged home from the hospital while receiving fondaparinux therapy.

A total of 2,213 patients were randomized and 2,184 were treated. Patients ranged in age from 18-97 years (mean age 62 years) with 44% men and 56% women. Patients were 94% Caucasian, 5% Black and 1% other races. For both groups, treatment continued for at least 5 days, and both

treatment groups received Vitamin K antagonist therapy initiated within 72 hours after the first study drug administration and continued for 90 ± 7 days, with regular dose adjustments to achieve an INR of 2-3. The primary efficacy endpoint was confirmed, symptomatic, recurrent VTE reported up to Day 97. Treatment with ARIXTRA® was associated with a VTE rate of 3.8% compared with a VTE rate of 5.0% for unfractionated heparin. The efficacy data are provided in Table 26 below.

Table 26 Efficacy of ARIXTRA® Injection in the Treatment of Pulmonary Embolism

Endpoint	**ARIXTRA®[1] 5, 7.5 or 10 mg SC once daily (Treatment Regimen)**	**Heparin[1] aPTT adjusted IV**
All Randomized PE Patients	N=1103	N=1110
Total VTE[2]	42[3] (3.8%)	56 (5.0%)
DVT only	12 (1.1%)	17 (1.5%)
Non-fatal PE	14 (1.3%)	24 (2.2%)
Fatal VTE	16 (1.5%)	15 (1.4%)

1 Patients were also treated with vitamin K antagonists initiated within 72 hours after the first study drug administration.
2 VTE was a composite of symptomatic recurrent VTE or fatal VTE reported up to Day 97.
3 The 95% confidence interval for the treatment difference for total VTE was: -3.0% to 0.5%.

Management of Unstable Angina or Non-ST Segment Elevation Myocardial Infarction (UA/NSTEMI)

In a randomized, double-blind, outcome trial, OASIS 5, 20,078 subjects presenting to hospital with suspected UA/NSTEMI acute coronary syndrome and at least 2 of 3 risk criteria (aged ≥60 years, troponin T or I or CK-MB above the upper limit of normal, or ECG changes compatible with ischemia) were randomized to ARIXTRA® (n=10,057) or enoxaparin (n=10,021) within 24 hours of the most recent episode of symptoms. Patients were to be eligible for anticoagulation treatment.

Table 27 Summary of Patient Demographics in OASIS 5 [1,2]

Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
Randomized, double-blind, non-inferiority outcome trial	2.5 mg fondaparinux SC once daily for up to 8 days or discharge 1 mg/kg enoxaparin SC twice daily (once daily if creatinine clearance was between 20 mL/min and 30 mL/min) for 2-8 days or until clinically stable	20078	67 (21-98)	62% men 38% women

[1] 45% of subjects had UA, and 55% had NSTEMI.

[2] Approximately 40% and 17% of patients had mild (creatinine clearance 50 to <80 mL/min) or moderate (creatinine clearance 30 to <50 mL/min) renal insufficiency, respectively, at randomization.

Patients received standard medical care for UA/NSTEMI including acetylsalicylic acid, clopidogrel/ ticlopidine, GPIIb/IIIa inhibitors, as well as percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery, where appropriate. Patients undergoing PCI received either a single pre-procedural dose of ARIXTRA® intravenously (ARIXTRA® treatment arm) or unfractionated heparin intravenously (enoxaparin treatment arm) using an algorithm based on the time of the previous subcutaneous dose and whether GPIIb/IIIa inhibitors were planned. Subcutaneous study drug was resumed after PCI if possible. Patients undergoing CABG surgery had study drug temporarily stopped 24 hours prior to surgery and restarted 48 hours post surgery, if possible.

The objective of the study was to determine whether ARIXTRA® was non-inferior to enoxaparin within 9 days of randomization based on the primary composite endpoint of death, myocardial infarction (MI) and refractory ischemia (RI) (see Table 28).

Table 28 Efficacy of ARIXTRA® in the Treatment of UA/NSTEMI up to Day 9 in OASIS 5 (All Randomized Patients)

Endpoint	ARIXTRA®[1] N=10 057	Enoxaparin[2] N=10 021	Hazard Ratio (95% CI)
Death or MI or RI[3]	579 (5.8%)	574 (5.7%)	1.01 (0.90, 1.13)[4]
Death	177 (1.8%)	186 (1.9%)	0.95 (0.77, 1.17)
MI	263 (2.6%)	264 (2.6%)	0.99 (0.84, 1.18)
RI	194 (1.9%)	189 (1.7%)	1.02 (0.84, 1.25)

1 Patients randomized to ARIXTRA® received 2.5 mg fondaparinux SC once daily for up to 8 days or discharge.
2 Patients randomized to enoxaparin sodium received 1 mg/kg enoxaparin SC twice daily (once daily if creatinine clearance was between 20 mL/min and 30 mL/min) for 2-8 days or until clinically stable.
3 The primary endpoint was a composite of death, myocardial infarction (MI) and refractory ischemia (RI) within 9 days of randomization.
4 p=0.003, one-sided non-inferiority.

ARIXTRA® was as effective as enoxaparin in reducing the risk of death, MI or refractory ischemia at Day 9 (see Table 28 and Table 29). The treatment effect observed for the components was consistent with that for the overall composite endpoint (see Table 28). At 6 month follow-up, the benefit of ARIXTRA® was maintained (Table 29).

Table 29 Efficacy of ARIXTRA® for the Prevention of Death, MI or RI in UA/NSTEMI up to Day 180 in OASIS 5 (All Randomized Patients)

Endpoint	ARIXTRA® [1] N=10 057	Enoxaparin[2] N=10 021	Hazard Ratio (95% CI)	P-value
Day 9[3]	579 (5.8%)	574 (5.7%)	1.019 (0.90, 1.13)	p=0.923[4]
Day 14	658 (6.5%)	701 (7.0%)	0.94 (0.84, 1.04)	p=0.222
Day 30	806 (8.0%)	865 (8.6%)	0.93 (0.84, 1.02)	p=0.127
Day 90	1044 (10.4%)	1112 (11.1%)	0.93 (0.86, 1.02)	p=0.110
Day 180	1223 (12.2%)	1309 (13.1%)	0.93 (0.86, 1.00)	p=0.063

1 Patients randomized to ARIXTRA® received 2.5 mg fondaparinux SC once daily for up to 8 days or discharge.
2 Patients randomized to enoxaparin sodium received 1 mg/kg enoxaparin SC twice daily (once daily if creatinine clearance was between 20 mL/min and 30 mL/min) for 2-8 days or until clinically stable.
3 The primary endpoint was a composite of death, myocardial infarction (MI) and refractory ischemia (RI) within 9 days of randomization.
4 p=0.003, one-sided non-inferiority.

In the management of UA/NSTEMI with ARIXTRA®, the risk of all cause mortality up to Day 180 is reported in Table 30.

Table 30 Efficacy of ARIXTRA® for the Prevention of All Cause Mortality in UA/NSTEMI up to Day 180 in OASIS 5 (All Randomized Patients)

Endpoint	ARIXTRA®[1] N=10 057	Enoxaparin[2] N=10 021	Hazard Ratio (95% CI)	P-value
Day 9	177 (1.8%)	186 (1.9%)	0.95 (0.77, 1.17)	0.614
Day 14	211 (2.1%)	242 (2.4%)	0.87 (0.72, 1.04)	0.135
Day 30	295 (2.9%)	352 (3.5%)	0.83 (0.71, 0.97)	0.022
Day 90	460 (4.6%)	510 (5.1%)	0.90 (0.79, 1.02)	0.089
Day 180	574 (5.7%)	638 (6.4%)	0.89 (0.80, 1.00)	0.052

[1] Patients randomized to ARIXTRA® received 2.5 mg fondaparinux SC once daily for up to 8 days or discharge.

[2] Patients randomized to enoxaparin sodium received 1 mg/kg enoxaparin SC twice daily (once daily if creatinine clearance was between 20 mL/min and 30 mL/min) for 2-8 days or until clinically stable.

The rates of major bleeding episodes for UA/NSTEMI patients treated with ARIXTRA® vs. enoxaparin are provided in Table 6 and Table 7 (see ADVERSE REACTIONS).

In patients undergoing PCI during the initial hospitalization, the relative effects of ARIXTRA® and enoxaparin on death, MI or refractory ischemia and on major bleeding at Day 9 were consistent with that observed for the overall population (see Table 31 and Table 32). However, in patients undergoing PCI, the incidence of guiding catheter thrombosis, although rare, was higher in patients treated with ARIXTRA® compared to enoxaparin (see WARNINGS AND PRECAUTIONS, Cardiovascular, and ADVERSE REACTIONS, *Management of UA/NSTEMI*, Risk of catheter thrombosis during PCI).

Table 31 Efficacy of ARIXTRA® by PCI Usage During Initial Hospitalisation up to Day 9 and Day 180 in OASIS 5 (All Randomized Patients)

		ARIXTRA®			Enoxaparin			HR (95% CI)
Death/MI/RI*		**n**	**N**	**%**	**n**	**N**	**%**	
Day 9	Overall	579	10057	5.8	574	10021	5.7	1.01 (0.90, 1.13)
PCI use:	Yes	305	3454	8.8	282	3435	8.2	1.08 (0.92, 1.27)
	No	274	6597	4.2	292	6585	4.4	0.94 (0.79, 1.10)
Day 180	Overall	1223	10057	12.2	1309	10021	13.1	0.93 (0.86, 1.00)
PCI use:	Yes	448	3454	13.0	438	3435	12.8	1.02 (0.89, 1.16)
	No	775	6597	11.7	871	6585	13.2	0.88 (0.80, 0.97)
Death/MI								
Day 9	Overall	409	10057	4.1	412	10021	4.1	0.99 (0.86, 1.13)
PCI use:	Yes	196	3454	5.7	185	3435	5.4	1.05 (0.86, 1.29)
	No	213	6597	3.2	227	6585	3.4	0.94 (0.78, 1.13)
Day 180	Overall	1042	10057	10.4	1127	10021	11.2	0.92 (0.84, 1.00)
PCI use:	Yes	332	3454	9.6	333	3435	9.7	0.99 (0.85, 1.16)
	No	710	6597	10.8	794	6585	12.1	0.89 (0.80, 0.98)
Death alone								
Day 9	Overall	177	10057	1.8	186	10021	1.9	0.95 (0.77, 1.17)
PCI use:	Yes	37	3454	1.1	38	3435	1.1	0.97 (0.62, 1.52)
	No	140	6597	2.1	148	6585	2.2	0.94 (0.75, 1.19)
Day 180	Overall	574	10057	5.7	638	10021	6.4	0.89 (0.80, 1.00)
PCI use:	Yes	113	3454	3.3	121	3435	3.5	0.93 (0.72, 1.20)
	No	461	6597	7.0	517	6585	7.9	0.89 (0.78, 1.01)

* The primary endpoint was a composite of death, myocardial infarction (MI) and refractory ischemia (RI) up to and including Day 9

Table 32 Adjudicated Major Bleeding by PCI Usage During Initial Hospitalisation (As Treated Patients) in OASIS 5

		ARIXTRA®			Enoxaparin			HR (95% CI)	P-value
		n	**N**	**%**	**n**	**N**	**%**		
On Therapy[1]	**Overall**	183	9979	1.8	389	9969	3.9	0.38 (0.29, 0.49)	<0.001
PCI use:	**Yes**	66	3422	1.9	165	3410	4.8	0.39 (0.29, 0.52)	
	No	117	6555	1.8	224	6559	3.4	0.51 (0.41, 0.64)	
Day 9	**Overall**	209	9979	2.1	406	9969	4.1	0.51 (0.43, 0.60)	<0.001
PCI use:	**Yes**	74	3422	2.2	169	3410	5.0	0.43 (0.33, 0.57)	
	No	135	6555	2.1	237	6559	3.6	0.57 (0.46, 0.70)	

[1] The on therapy period was from the start of dosing at randomization until 2 days post the last injection.

Management of ST segment Elevation Myocardial Infarction (STEMI)

In OASIS 6 a randomized, double-blind, outcome trial, , ARIXTRA® was compared to usual care (placebo or UFH) in 12,092 subjects presenting to hospital with STEMI acute coronary syndrome within 12 hours of symptom onset. Randomization was stratified according to whether UFH was indicated based on the judgement of the investigator. A total of 5,658 patients were enrolled in Stratum 1 who received ARIXTRA® (n=2,823) or placebo (n=2,835) and 6,434 patients were enrolled in Stratum 2 who received ARIXTRA® (n=3,213) or UFH (n=3,221).

Table 33 Summary of Patient Demographics in OASIS 6[1]

Trial design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
Randomized, double-blind, superiority outcome trial	2.5 mg fondaparinux SC once daily for up to 8 days or discharge, initial dose 2.5 mg IV bolus Usual care Stratum 1: placebo Stratum 2: UFH 60 IU/kg IV bolus followed by 12 IU/kg/hr infusion for 24-48 hours (IV bolus only in primary PCI patients)	12 092	61 (22-96)	72% men 28% women

[1] Approximately 40% and 14% of patients had mild (creatinine clearance 50 to <80 mL/min) or moderate (creatinine clearance 30 to <50 mL/min) renal insufficiency, respectively, at randomization.

The primary adjudicated endpoint was a composite of death and reinfarction (recurrent myocardial infarction) within 30 days of randomization. The results for ARIXTRA® compared to control (UFH or placebo combined) at Day 30 were 9.7% vs. 11.1% for death or myocardial reinfarction (p=0.008), 7.8% vs. 8.9% for death (all cause mortality) (p=0.023), and 2.3% vs. 2.8% for myocardial reinfarction (p=0.069) (see Table 34).

Table 34 Efficacy of ARIXTRA® in the Treatment of STEMI up to Day 30 in OASIS 6 (All Randomized Patients)

	Overall			Stratum 1			Stratum 2		
Endpoint	**ARIXTRA[1]** N=6036	**Control[2]** N=6056	**Hazard Ratio[3]** (95% CI)	**ARIXTRA** N=2823	**Placebo[5]** N=2835	**Hazard Ratio[3]** (95% CI)	**ARIXTRA** N=3213	**UFH** N=3221	**Hazard Ratio[3]** (95% CI)
Death/ Reinfarction[4]	584 (9.7%)	675 (11.1%)	0.86 (0.77, 0.96)	318 (11.3%)	396 (14.0%)	0.80 (0.60, 0.93)	266 (8.3%)	279 (8.7%)	0.94 (0.79, 1.11)
Death	470 (7.8%)	541 (8.9%)	0.87 (0.77, 0.98)	257 (9.1%)	321 (11.3%)	0.80 (0.68, 0.94)	213 (6.6%)	220 (6.8%)	0.95 (0.79, 1.15)
Reinfarcton	141 (2.3%)	172 (2.8%)	0.81 (0.65, 1.02)	74 (2.6%)	92 (3.2%)	0.79 (0.58, 1.07)	67 (2.1%)	80 (2.5%)	0.83 (0.60, 1.15)

[1] Patients randomized to ARIXTRA® received an IV bolus injection of 2.5 mg followed by 2.5 mg by SC injection daily for up to 8 days or discharge.
[2] Patients randomized to UFH received an IV bolus injection 60 IU/kg followed by an infusion of 12 IU/kg/hr for 24 to 48 hours.
[3] The hazard ratio, ARIXTRA® versus control, was adjusted for treatment group and strata.
[4] The primary endpoint was a composite of death and reinfarction within 30 days of randomization.
[5] Placebo patients did not receive unfractionated heparin as an anticoagulant.

The treatment effect was greater with ARIXTRA® than with control (UFH or placebo combined) in reducing the risk of death or reinfarction at Day 30 (see Table 34). The treatment effect observed for the components was consistent with that for the overall composite endpoint (see Table 34). At 6 month follow-up, the benefit of ARIXTRA® was maintained (see Table 35).

Table 35 Efficacy of ARIXTRA® for the Prevention of Death or Reinfarction in STEMI up to 6 Months in OASIS 6 (All Randomized Patients)

	Overall			Stratum 1			Stratum 2		
Endpoint	**ARIXTRA[1]** N=6036	**Control[2]** N=6056	**Hazard Ratio[3]** (95% CI)	**ARIXTRA** N=2823	**Placebo[4]** N=2835	**Hazard Ratio[3]** (95% CI)	**ARIXTRA** N=3213	**UFH[2]** N=3221	**Hazard Ratio[3]** (95% CI)
Day 9	443 (7.3%)	536 (8.9%)	0.82 (0.73, 0.93)	240 (8.5%)	314 (11.1%)	0.76 (0.64, 0.90)	203 (6.3%)	222 (6.9%)	0.91 (0.75, 1.10)
Day 30	584 (9.7%)	675 (11.1%)	0.86 (0.77, 0.96)	318 (11.3%)	396 (14.0%)	0.80 (0.69, 0.93)	266 (8.3%)	279 (8.7%)	0.94 (0.79, 1.11)
Day 90	683 (11.3%)	796 (13.1%)	0.85 (0.77, 0.94)	369 (13.1%)	441 (15.6%)	0.83 (0.72, 0.95)	314 (9.8%)	355 (11.0%)	0.87 (0.75, 1.02)
Day 180	756 (12.5%)	855 (14.1%)	0.88 (0.79, 0.97)	414 (14.7%)	469 (16.5%)	0.87 (0.77, 1.00)	342 (10.6%)	386 (12.0%)	0.87 (0.75, 1.01)

[1] Patients randomized to ARIXTRA® received an IV bolus injection of 2.5 mg followed by 2.5 mg by SC injection daily for up to 8 days or discharge.
[2] Patients randomized to UFH received an IV bolus injection 60 IU/kg followed by an infusion of 12 IU/kg/hr for 24 to 48 hours.
[3] The hazard ratio, ARIXTRA® versus control, was adjusted for treatment group and strata.
[4] Placebo patients did not receive unfractionated heparin as an anticoagulant.

In the management of STEMI with ARIXTRA®, the risk of all cause mortality up to Day 180 is reported in Table 36.

Table 36 Efficacy of ARIXTRA® for the Prevention of Adjudicated Death (All Cause Mortality) in STEMI up to 6 months in OASIS 6 (All Randomized Patients)

	Overall			Stratum 1			Stratum 2		
Endpoint	**ARIXTRA[1]** N=6036	**Control[2]** N=6056	**Hazard Ratio[3]** (95% CI)	**ARIXTRA** N=2823	**Placebo[4]** N=2835	**Hazard Ratio[3]** (95% CI)	**ARIXTRA** N=3213	**UFH** N=3221	**Hazard Ratio[3]** (95% CI)
Day 9	368 (6.1%)	426 (7.0%)	0.86 (0.75, 0.99)	202 (7.2%)	252 (8.9%)	0.80 (0.66, 0.96)	166 (5.2%)	174 (5.4%)	0.95 (0.77, 1.17)
Day 30	470 (7.8%)	541 (8.9%)	0.87 (0.77, .98)[6]	257 (9.1%)	321 (11.3%)	0.80 (0.68, 0.94)	213 (6.6%)	220 (6.8%)	0.95 (0.79, 1.15)
Day 90	545 (9.0%)	634 (10.5%)	0.86 (0.76, 0.96)	301 (10.7%)	354 (12.5%)	0.85 (0.73, 0.99)	244 (7.6%)	280 (8.7%)	0.86 (0.72, 1.02)
Day 180	599 (9.9%)	675 (11.1%)	0.88 (0.79, 0.99)	336 (11.9%)	375 (13.2%)	0.89 (0.77, 1.04)	263 (8.2%)	300 (9.3%)	0.87 (0.73, 1.02)

[1] Patients randomized to ARIXTRA® received an IV bolus injection of 2.5 mg followed by 2.5 mg by SC injection daily for up to 8 days or discharge.

[2] Patients randomized to UFH received an IV bolus injection 60 IU/kg followed by an infusion of 12 IU/kg/hr for 24 to 48 hours.

[3] The hazard ratio, ARIXTRA® versus control, was adjusted for treatment group and strata.

[4] Placebo patients did not receive unfractionated heparin as an anticoagulant.

The results for the primary endpoint (death or reinfarction) at Day 30 by reperfusion strategy are presented in Table 37.

Table 37 Efficacy of ARIXTRA® for the Prevention of Adjudicated Death or Reinfarction in STEMI up to Day 30 in OASIS 6 by Initial Reperfusion Strategy (All Randomized Patients)

Endpoint	ARIXTRA® (N=6036)	Control (N=6056)	Hazard Ratio (95% CI)
Overall (primary endpoint)	584 (9.7%)	675 (11.1%)	0.86 (0.77, 0.96) [1]
Reperfusion Strategy			
No reperfusion	176/1452 (12.1%)	211/1405 (15.0%)	0.79 (0.65, 0.97)
Thrombolytic Agent	295/2695 (10.9%)	373/2742 (13.6%)	0.79 (0.68, 0.93)
- Fibrin specific	50/425 (11.8%)	54/443 (12.2%)	0.98 (0.67, 1.44)
- Non-fibrin specific	244/2267 (10.8%)	318/2298 (13.8%)	0.77 (0.65, 0.90)
Primary PCI	113/1889 (6.0%)	91/1909 (4.8%)	1.26 (0.96, 1.66)
Patients receiving Thrombolytics or No reperfusion[2]			
Overall	471/4147 (11.4%)	584/4147 (14.1%)	0.80 (0.70, 0.90)
- Stratum 1[3]:	318/2813 (11.3%)	395/2828 (14.0%)	0.80 (0.69, 0.92)
- Stratum2[4]	153/1334 (11.5%)	189/1319 (14.3%)	0.79 (0.64, 0.98)

[1] p-value versus control: 0.008
[2] Patients not undergoing primary PCI
[3] UFH Not Indicated
[4] UFH Indicated

The rates of major bleeding episodes for STEMI patients treated with ARIXTRA® vs. control (UFH/placebo) are provided in Table 9 (see ADVERSE REACTIONS).

The results for major bleeding by initial reperfusion strategy are presented in Table 38.

Table 38 Major Bleeding in the OASIS 6 Study by Initial Reperfusion Strategy (As Treated Patients)

Endpoint	ARIXTRA®	Control	Hazard Ratio (95% CI)
On-therapy			
Overall	99/5954 (1.7)	120/5947 (2.0)	0.82 (0.63, 1.07)
Reperfusion Strategy			
No reperfusion	16/1415 (1.1)	24/1367 (1.8)	0.64 (0.34, 1.20)
Thrombolytic Agent	47/2676 (1.8)	66/2711 (2.4)	0.72 (0.49, 1.04)
- Fibrin specific	10/420 (2.47)	18/443 (4.2)	0.58 (0.27, 1.26)
- Non-fibrin specific	37/2253 (1.6)	48/2277 (2.1)	0.77 (0.50, 1.18)
Primary PCI	36/1863 (1.9)	30/1869 (1.6)	1.21 (0.74, 1.96)
Patients receiving Thombolytics or No reperfusion[1]			
Overall	63/4091 (1.5)	90/4078 (2.2)	0.69 (0.50, 0.95)
- Stratum 1 [2]	40/2802 (1.4)	53/2813 (1.9)	0.75 (0.50, 1.13)
- Stratum 2 [3]	23/1289 (1.8)	37/1265 (2.9)	0.61 (0.36, 1.02)
By Day 9			
Overall	104/5954 (1.7)	128/5947 (2.1)	0.81 (0.62, 1.05)
Reperfusion Strategy			
No reperfusion	17/1415 (1.2)	24/1367 (1.8)	0.68 (0.36, 1.26)
Thrombolytic Agent	47/2676 (1.8)	73/2711 (2.7)	0.65 (0.45, 0.93)
- Fibrin specific	10/420 (2.4)	18/433 (4.2)	0.58 (0.27, 1.26)
- Non-fibrin specific	37/2253 (1.6)	55/2277 (2.4)	0.67 (0.44, 1.01)
Primary PCI	40/1863 (2.1)	31/1869 (1.7)	1.30 (0.81, 2.08)
Patients receiving Thombolytics or No reperfusion[1]			
Overall	64/4091 (1.6)	97/4078 (2.4)	0.65 (0.47, 0.89)
- Stratum 1 [2]	39/2802 (1.4)	58/2813 (2.1)	0.67 (0.45, 1.00)
- Stratum 2 [3]	25/1289 (1.9)	39/1265 (3.1)	0.63 (0.38, 1.03)

[1] Patients not undergoing primary PCI
[2] UFH Not Indicated
[3] UFH Indicated

14 NON-CLINICAL TOXICOLOGY

Acute Toxicity

Single subcutaneous or intravenous doses of 40 mg/kg were well tolerated in mice, rats and monkeys. No lethal effects were observed. This dose represents up to 1200 times the recommended human dose.

Long Term Toxicity

Repeated dose toxicity studies were performed in rats and monkeys at dose levels of 0.4, 2 and 10 mg/kg/d, up to 12, 60 and 300 times the recommended human doses. Fondaparinux had low toxicity and induced mainly an increase of the trauma-related hemorrhage.

Small numbers of animal deaths were due to hemorrhage and hematomas. These were primarily attributed to repeated injection traumas and to the pharmacological activity of the compound.

In monkey studies, some large hematomas were also observed at handling sites, blood puncture and anaesthetic injection sites.

Carcinogenicity

Fondaparinux has not been tested for its carcinogenic potential in long-term animal studies.

Mutagenicity

Fondaparinux was not mutagenic in the *in vitro* Ames Test nor the mouse lymphoma cell ($L5178Y/TK^{+/-}$) forward mutation test. Fondaparinux was not clastogenic in the human lymphocyte chromosomal aberration test, rat hepatocyte unscheduled DNA synthesis (UDS) test or in the *in vivo* rat micronucleus test.

Reproduction and Teratology

Fondaparinux at doses up to 10 mg/kg/day (i.e. doses up to 280 times the human daily doses) did not impair the reproduction parameters studied: rat mating performance and fertility, rat and rabbit gestation and embryo-fetal development and rat parturition, lactation, new-born viability and growth, F1 behaviour and reproduction and F2 fetal development.

The main treatment-related findings were hematomas and hemorrhage at the injection site. The only other treatment-related finding noted was one fatality associated with hematoma and changes in liver and lungs.

Very low placental transfer and very limited excretion in the milk were demonstrated in rats.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

PrARIXTRA®
Fondaparinux Sodium injection

Read this carefully before you start taking ARIXTRA and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about ARIXTRA.

What is ARIXTRA used for?

- ARIXTRA® helps prevent clots from forming in the blood vessels of the legs or lungs in patients undergoing:
    - knee, hip replacement or hip fracture surgeries. ARIXTRA® can be used for up to one month after these types of surgeries.
    - abdominal surgery.
- ARIXTRA® is used to treat blood clots in a deep vein of the legs and in the blood vessels of the lungs.
- ARIXTRA® is used to manage severe chest pain, a specific type of heart attack (non ST segment myocardial infarction) and a severe heart attack.

It is not known if ARIXTRA is safe and effective in children under the age of 17.

Due to the risk of bleeding, ARIXTRA will be used with caution in patients who 65 years of age and older.

How does ARIXTRA work?

ARIXTRA is synthetic and it blocks a specific clotting factor. It helps to prevent the development of unwanted blood clots (thrombosis) in blood vessels.

What are the ingredients in ARIXTRA?

Medicinal ingredients: Fondaparinux sodium

Non-medicinal ingredients: Isotonic solution of sodium chloride, water for injection and, if necessary, sodium hydroxide or hydrochloric acid for pH adjustment. The needle shield of the pre-filled syringe contains dry natural latex rubber.

ARIXTRA comes in the following dosage form:

ARIXTRA is a solution for injection. It is supplied in sterile, single use pre-filled syringes in packages of 10. ARIXTRA comes in the following strengths:

- 2.5 mg/0.5 mL;
- 5 mg/0.4 mL*;
- 7.5 mg/0.6 mL;

- 10 mg /0.8 mL*.

** Strengths not available in Canada.*

Do not use ARIXTRA if:

- You are allergic to fondaparinux sodium or to any of the non-medicinal ingredients in ARIXTRA.
- You have an abnormally low number of platelets in your blood (thrombocytopenia) and a positive lab result for a specific test. Your healthcare professional will tell you if this applies to you;
- You are bleeding excessively;
- You have a bacterial infection in your heart.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you use ARIXTRA. Talk about any health conditions or problems you may have, including if:

- You have an allergy to latex;
- You are bleeding excessively;
- You are at risk of uncontrolled bleeding because you:
    - are 65 years of age or older;
    - weigh less than 50 kg;
    - have a stomach ulcer;
    - have a bleeding disorder;
    - had recent bleeding in your brain;
    - had recent brain, spinal column or eye surgery;
    - have kidney or liver disease.
- You are taking other medications that may increase your risk of bleeding, such as:
    - nonsteroidal anti-inflammatory drugs (NSAIDS)
    - platelet inhibitors
- You are pregnant or planning to become pregnant or are breast-feeding. It is not known if ARIXTRA may cause harm to your fetus or nursing baby.

Other warnings you should know about:

- Don’t stop using ARIXTRA until your healthcare professional tells you to. Contact your healthcare professional immediately if you feel you need to stop taking ARIXTRA (e.g. if you have developed bleeding).
- Like other blood thinners, ARIXTRA may result in serious or life-threatening bleeding from any site, including internal organs.
- You should only use ARIXTRA as an injection under your skin (subcutaneous). It is not safe to inject ARIXTRA into your muscle (intramuscular).
- The timing of the first ARIXTRA injection is very specific, depending on the condition you have. Your healthcare professional will make sure they give you the first dose at the right time to help prevent bleeding. Always follow your healthcare professionals’ instructions for how to use ARIXTRA.
- Your healthcare professional will monitor you if the number of platelets in your blood decreases (thrombocytopenia) while you are taking ARIXTRA.
- Your healthcare professional will monitor your kidney function if you’ve had abdominal,

knee, hip replacement or hip fracture surgeries.

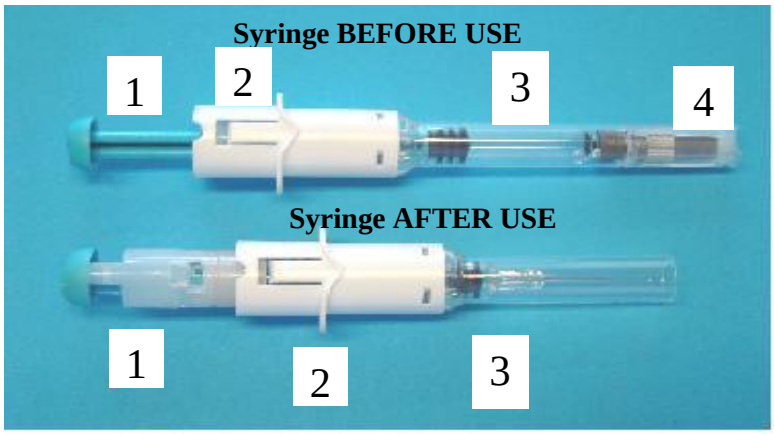
- ARIXTRA is not recommended if you have severe kidney problems.
- Give yourself time after injecting ARIXTRA to see how you feel before driving a vehicle or using machinery

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to use ARIXTRA:

- Always use ARIXTRA as directed by your healthcare professional. Check with healthcare professional if you are unsure.
- Don't stop using ARIXTRA until your healthcare professional tells you to. Contact your healthcare professional if you feel you need to stop taking ARIXTRA.
- ARIXTRA is given by injection under the skin (subcutaneously) into a skin fold of the lower stomach area. Do not inject ARIXTRA into muscle (intramuscularly). The next section includes a step-by-step 'Instructions for use' guide.
- While you are in the hospital, a healthcare professional will give your first injection. You may need to continue your injections of ARIXTRA after you return home.

The different parts of ARIXTRA safety syringe are:



1 - Plunger
2 - Finger-grip
3 - Security sleeve
4 - Rigid needle shield

Instructions for self-injection of ARIXTRA:

I. Before Injecting:

1. Inspect the solution in the syringe. Do not use if the solution is hazy, has particles in it, is discolored or is leaking.
2. Wash your hands thoroughly with soap and water. Towel dry.
3. Sit or lie down in a comfortable position. Choose a spot in the lower stomach area, at least 5 cm from your belly button (Figure 1), for your injection. If you can't inject in the stomach area, consult your healthcare professional for instructions.
4. Do not press on the plunger prior to injection.

Figure 1

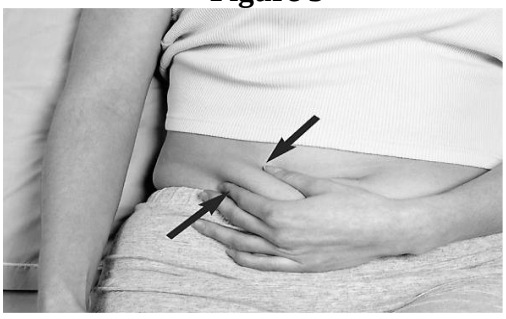
II. When ready to inject:

1. Clean the injection area with an alcohol swab.
2. Hold the body of the syringe firmly in one hand.
3. Remove the needle shield by first twisting it and then pulling it in a straight line away from the body of syringe (Figure 2). Discard the needle shield.
4. **Important:**
   i. Do not touch the needle or allow it to come into contact with any surface prior to the injection.
   ii. The presence of a small air bubble in the syringe is normal.
   iii. Do not try to remove this air bubble before making the injection in order to be sure that you do not lose any product.

Figure 2

5. Gently pinch the skin that has been cleaned to make a fold. Hold the fold between the thumb and the forefinger during the entire injection (Figure 3).
6. Alternate the left and right side of the stomach at each injection.

Figure 3

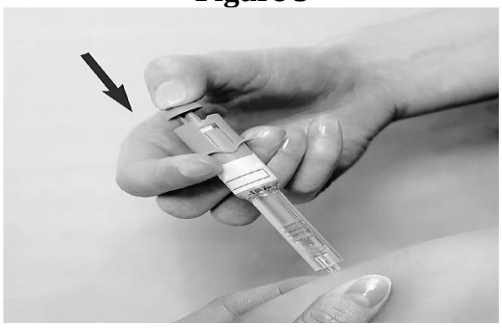


7. With the other hand, hold the syringe firmly by the finger grip. Insert the full length of the needle perpendicularly (at an angle of 90°) into the skin fold (Figure 4).

Figure 4

8. **Inject ALL of the contents of the syringe by pressing down on the plunger as far as it goes.** This will activate the automatic needle protection system (Figure 5).

Figure 5



9. Release the plunger and the needle will withdraw automatically from the skin and retract into the security sleeve where it will be locked permanently (Figure 6).
10. Discard the used syringe into a sharps container as your nurse or doctor has instructed you.

Figure 6

Usual dose:

- For prevention of blood clots following orthopedic or abdominal surgery:
    - The usual dose of ARIXTRA (fondaparinux sodium) is 2.5 mg once a day.

- For treatment of blood clots:
    - The usual dose of ARIXTRA is 5 mg (body weight less than 50 kg), 7.5 mg (body weight 50-100 kg) or 10 mg (body weight greater than 100 kg) once daily.

- In the management of heart attacks or severe angina:
    - The usual dose of ARIXTRA is 2.5 mg once daily. Your first dose may be given by intravenous injection, depending on your condition.

Overdose:

If you think you have injected too much ARIXTRA, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
NEVER inject a double dose to make up for forgotten individual doses. If you are not sure what to do, ask your doctor or pharmacist before you take any action.

What are possible side effects from using ARIXTRA?
These are not all the possible side effects you may feel when taking ARIXTRA. If you experience any side effects not listed here, contact your healthcare professional.

As ARIXTRA acts on the blood clotting system, many of the side effects are related to signs of bruising or bleeding. Although rare, some patients had major bleeding that lead to death.

ARIXTRA may also cause some side effects which can only be diagnosed by your health care provider and may require blood tests. Examples include:
- decrease or increase in the number of platelets (blood cells necessary for blood clotting)
- abnormal blood clotting (coagulation disorder)
- bleeding around the brain or internal organs.

Common side effect that may occur: insomnia (trouble sleeping).

An uncommon side effect that may occur: headache

Rare side effects that may occur:
- anxiety
- confusion
- dizziness
- coughing
- indigestion
- stomach pain
- constipation
- diarrhea
- skin reactions at injection site (mild irritation, pain, bruising and redness)
- tiredness
- flushing
- drowsiness

- vertigo (feeling of spinning)
- shortness of breath

Serious side effects and what to do about them			
Symptom / effect	**Talk with your doctor or pharmacist**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Very Common A low number of red blood cells which can cause tiredness, weakness, shortness of breath and feeling generally unwell	X		
Bleeding from various sites (i.e., from an operation site, bruising, blood in urine and stool, an existing stomach ulcer, nosebleed, etc.)		X	
Bruises that are joining together	X		
Urinary tract infection (pain or burning sensation during urination, frequent urge to urinate)		X	
Common Liver problems (symptoms include nausea, vomiting, loss of appetite, yellowing of the skin or eyes, dark urine and unusual tiredness)		X	
Syncope (loss of consciousness)		X	
Edema (swelling)		X	
Rare Wound infection at site of surgery (oozing of fluid, swelling around the wound)		X	

Allergic reactions such as rash or itching, swelling (usually of the face, lips, tongue or throat) which may cause difficulty breathing or swallowing or collapse			X
Reduction of potassium in the blood (hypokalemia) which can cause muscular weakness and cramping		X	
Low blood pressure (if measured) which can result in light-headedness, dizziness or fainting		X	
Common Syncope (loss of consciousness)		X	
Chest pain		X	
Leg pain		X	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected adverse reactions associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
ARIXTRA should be stored below 25°C. Do not freeze.
Do not use ARIXTRA under the following conditions:

- after the expiry date stated on the label and carton;
- if you notice that particulate matter or discoloration is present in the solution;
- if you notice that the syringe is damaged;
- if you have opened a syringe and do not intend to use it straight away.

Any unused syringe should be disposed of in a safe manner.

Keep out of the reach and sight of children.

If you want more information about ARIXTRA:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp); the manufacturer's website www.aspenpharma.ca, or by calling 1-844-330-1213.

This leaflet was prepared by
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Last revised: July 19, 2019

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