

AUSTRALIAN PRODUCT INFORMATION

ARIXTRA (FONDAPARINUX SODIUM)

SOLUTION FOR INJECTION

1 NAME OF THE MEDICINE

Fondaparinux sodium (INN)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled automatic safety syringe 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 and water for Injections.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Solution for injection

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ARIXTRA is indicated for the prevention of venous thromboembolic events (VTE) in patients undergoing major orthopaedic surgery of the lower limbs such as hip fracture, major knee or hip replacement surgery.

ARIXTRA is indicated for the prevention of venous thromboembolic events (VTE) in patients undergoing abdominal surgery who are at risk of thromboembolic complications.

ARIXTRA is indicated for the treatment of acute deep venous thrombosis (DVT) and acute pulmonary embolism (PE).

ARIXTRA is indicated for the treatment of unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI) in patients for whom urgent (<120 min) invasive management (PCI) is not indicated.

ARIXTRA is indicated for the treatment of ST segment elevation myocardial infarction (STEMI) in patients who are managed without any form of initial reperfusion therapy.

4.2 DOSE AND METHOD OF ADMINISTRATION

ADULTS

Prophylaxis of VTE

The recommended dose of ARIXTRA is 2.5 mg once daily administered post-operatively by subcutaneous injection.

The initial dose should be given 6 hours following surgical closure provided that haemostasis has been established. Administration before 6 hours has been associated with an increased risk of major bleeding.

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Treatment should be continued for at least 7 ± 2 days. For orthopaedic surgery cases where the risk of VTE persists, treatment can be extended for as long as indicated up to a maximum of 31 days of therapy.

For information pertaining to patients aged ≥ 75 years or those with moderate or severe renal impairment, or hepatic impairment refer to the section below.

Treatment of Acute DVT and PE

The recommended dose of ARIXTRA is 7.5 mg (patients with body weight ≥ 50 , ≤ 100 kg) once daily administered by subcutaneous injection. For patients with body weight < 50 kg, the recommended dose is 5 mg. For patients with body weight > 100 kg, the recommended dose is 10 mg.

Treatment should be continued for at least 5 days and until adequate oral anticoagulation is established (INR 2 to 3). Concomitant oral anticoagulation treatment should be initiated as soon as possible and usually within 72 hours. The average duration of administration in clinical trials was 7 days.

For information pertaining to patients aged ≥ 75 years or those with moderate or severe renal impairment, or hepatic impairment refer to the section below.

Treatment of unstable angina/non-ST segment elevation myocardial infarction (UA/NSTEMI)

The recommended dose of fondaparinux is 2.5 mg once daily, administered by subcutaneous injection.

Treatment should be initiated as soon as possible following diagnosis and continued for up to a maximum of 8 days or until hospital discharge if that occurs earlier.

If a patient is to undergo percutaneous coronary intervention (PCI), unfractionated heparin (UFH) as per standard practice should be administered during PCI, taking into account the patient's potential risk of bleeding, including the time since the last dose of fondaparinux (see Section 4.4 Special warnings and precautions for use). The timing of restarting subcutaneous fondaparinux after sheath removal should be based on clinical judgment. In the pivotal UA/NSTEMI clinical trial, treatment with fondaparinux was restarted no earlier than 2 hours after sheath removal.

Treatment of ST segment elevation myocardial infarction (STEMI)

The recommended dose of fondaparinux is 2.5 mg once daily. The first dose of fondaparinux 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 a maximum of 8 days or until hospital discharge if that occurs earlier.

If a patient is to undergo non-primary PCI, unfractionated heparin (UFH) as per standard practice should be administered during PCI, taking into account the patient's potential risk of bleeding, including the time since the last dose of fondaparinux (see Section 4.4 Special warnings and precautions for use). The timing of restarting subcutaneous fondaparinux after sheath removal should be based on clinical judgment. In the pivotal STEMI clinical trial, treatment with fondaparinux was restarted no earlier than 3 hours after sheath removal.

Patients who are to undergo coronary artery bypass graft (CABG) surgery

In STEMI or UA/NSTEMI 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.

SPECIAL POPULATIONS

Prophylaxis of VTE

Timing of the first ARIXTRA dose requires strict adherence in patients ≥ 75 years (elderly patients may show reduced elimination of fondaparinux), and/or with body weight < 50 kg and/or with moderate renal impairment (creatinine clearance 30 – 50 mL/min).

The first ARIXTRA dose should be given not earlier than 6 hours following surgical closure. The injection should not be given unless haemostasis has been established (see Section 4.4 Special warnings and precautions for use). No dosage adjustment is necessary.

Paediatrics

The safety and efficacy of fondaparinux in patients under the age of 17 years has not been established.

Use in the Elderly

Elderly patients aged ≥ 75 years including those with a body weight < 50 kg and/or moderate renal impairment (creatinine clearance 30-50 mL/min) may show reduced elimination of fondaparinux. This may increase the risk of haemorrhage in elderly patients receiving ARIXTRA (see Section 4.4 Special warnings and precautions for use).

Low body weight

Patients with body weight < 50 kg are at increased risk of bleeding. Elimination of fondaparinux decreases with weight. Fondaparinux should be used with caution in these patients (see Section 4.4 Special warnings and precautions for use).

Use in Patients with Moderate/Severe Renal Impairment

Prophylaxis of VTE and Treatment of Acute DVT and PE

ARIXTRA should not be used in patients with severe renal impairment (creatinine clearance less than 30 mL/min) (see Section 4.3 Contraindications).

In patients with moderate renal impairment, ARIXTRA should be used with care (see Section 4.4 Special warnings and precautions for use).

Treatment of UA/NSTEMI and STEMI

Fondaparinux should not be used in patients with creatinine clearance < 30 mL/min (see Section 4.3 Contraindications). No dosage reduction is required for patients with creatinine clearance > 30 mL/min.

Use in Patients with Hepatic Impairment

No dosing adjustment is necessary in patients with mild to moderate hepatic impairment since there is no evidence that fondaparinux is metabolised or eliminated in bile. In patients with severe hepatic impairment, ARIXTRA should be used with care (see Section 4.4 Special warnings and precautions for use).

METHOD OF ADMINISTRATION

ARIXTRA is administered by subcutaneous injection. It contains no antimicrobial agent. ARIXTRA is for single use in one patient only. Discard any residue.

Parenteral solutions should be inspected visually for particulate matter and discoloration prior to administration.

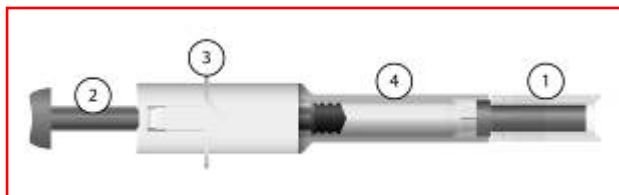
Intravenous administration should be through an existing intravenous line either directly or using a small volume (25 or 50 mL) 0.9% saline mini-bag. To avoid the loss of medicinal product when using the pre-filled syringe do not expel the air bubble from the syringe before the injection. The intravenous tubing should be well flushed with saline after injection to ensure that all of the medicinal product is administered. If administered via a mini-bag, the infusion should be given over 1 to 2 minutes.

The sites of subcutaneous injection should alternate between the left and the right anterolateral and left and right posterolateral abdominal wall. To avoid the loss of medicinal product when using the pre-filled syringe do not expel the air bubble from the syringe before injection. The whole length of the needle should be inserted between the thumb and forefinger (see figures 2 and 3). The skin fold should be held throughout the injection.

ARIXTRA is intended for use under a physician's guidance. Patient's 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. Instructions for self-administration are included below.

The parts of the syringe with an automatic needle protection system are:

- Needle shield
- Plunger
- Finger-grip
- Security sleeve



To use the ARIXTRA syringe, remove the needle shield, by first twisting it and then pulling it straight off (figure 1).

Discard the needle shield.



Figure 1

For subcutaneous administration:

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 2).



Figure 2

Insert the full length of the needle perpendicularly (at an angle of 90°) into the skin fold (figure 3).



Figure 3

Inject ALL of the content of the syringe by pressing down on the plunger as far as it goes (figure 4), and then release it: the needle will withdraw automatically from the skin into a security sleeve and then will be locked permanently (figure 5).



Figure 4



Figure 5

Discard the used syringe in a safe manner.

4.3 CONTRAINDICATIONS

Severe renal impairment (creatinine clearance <30 mL/min). Fondaparinux is eliminated primarily by the kidneys and the risk of haemorrhage may increase with renal impairment. Also see Section 4.4 Special warnings and precautions for use – Use in renal Impairment.

Active major bleeding

Known hypersensitivity to fondaparinux sodium

Acute bacterial endocarditis

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Fondaparinux must not be administered intramuscularly.

Haemorrhage

ARIXTRA, like other anti-thrombotic medicinal products, must be used with caution in patients who have an increased risk of haemorrhage, such as those with congenital or acquired bleeding disorders, active ulcerative gastrointestinal disease, recent intracranial haemorrhage, shortly after brain, spinal or ophthalmic surgery, and in patients treated concomitantly with anti-platelet drugs. If co-administration is essential, close monitoring may be appropriate. In the pivotal clinical studies, the percentages of patients with adjudicated bleeding events are shown in the ADVERSE EFFECTS section (Table 1 to Table 3).

Prevention and treatment of VTE

Other medicinal products enhancing the risk of haemorrhage, with the exception of vitamin K antagonists used concomitantly for treatment of VTE, should not be administered with fondaparinux. If co-administration is essential, close monitoring of the patient is recommended (see Section 4.5 Interactions with other medicines and other forms of interactions).

Prevention of VTE following surgery (timing of first fondaparinux injection)

The timing of the first injection requires strict adherence. The first dose should be given no earlier than 6 hours following surgical closure, and only after haemostasis has been established. Administration before 6 hours has been associated with an increased risk of major bleeding. Patient groups at particular risk are those from 75 years of age, body weight of less than 50 kg, or renal impairment with creatinine clearance less than 50 ml/min

For treatment of UA/NSTEMI and STEMI

Fondaparinux should be used with caution in patients who are being treated concomitantly with other agents that increase the risk of haemorrhage (such as GPIIb/IIIa inhibitors or thrombolytics).

PCI and risk of guiding catheter thrombus

In STEMI patients undergoing primary PCI, the use of fondaparinux prior to and during PCI is not recommended. Similarly, in UA/NSTEMI patients with life threatening conditions that require urgent revascularisation, the use of fondaparinux prior to and during PCI is not recommended. These are patients with refractory or recurrent angina associated with dynamic ST deviation, heart failure, life-threatening arrhythmias or haemodynamic instability.

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In UA/NSTEMI and STEMI patients undergoing non-primary PCI, the use of fondaparinux as the sole anticoagulant during PCI is not recommended due to an increased risk of guiding catheter thrombus (see Section 5.1 Pharmacodynamic properties - Clinical trials and section 4.8 Adverse effects (Undesirable effects) -*Catheter-related thrombosis*). Therefore, adjunctive UFH should be used during non-primary PCI according to standard practice (see Section 4.2 Dose and method of administration).

Spinal/Epidural anaesthesia

As with other anti-thrombotic medicinal products, epidural or spinal haematomas may occur with concurrent use of ARIXTRA and spinal/epidural anaesthesia or spinal puncture. Such complications can result in long-term or permanent paralysis. The risk of these events is increased by the use of indwelling epidural catheters for administration of analgesia or by the concomitant use of drugs affecting haemostasis such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, or other anticoagulants. The risk also appears to be increased by traumatic or repeated epidural or spinal puncture.

There is no clinical experience with the use of ARIXTRA in patients requiring an indwelling catheter for spinal anaesthesia for periods greater than six hours.

If the patient is given anticoagulation in the context of epidural/spinal anaesthesia extreme vigilance and frequent monitoring is required to detect any signs and symptoms of spinal haematoma such as midline back pain, sensory and motor deficits (numbness, weakness, or paralysis in the lower limbs, bowel and/or bladder dysfunction). If signs or symptoms of spinal haematoma are suspected, urgent diagnosis and treatment should be initiated. Patients should be instructed to inform their doctor immediately if they experience any of the above signs or symptoms.

Low body weight

Patients with body weight < 50 kg are at increased risk of bleeding. Elimination of fondaparinux decreases with decreasing body weight. Fondaparinux should be used with caution in these patients (see Section 4.2 Dose and method of administration).

Thrombocytopenia

Until further experience with fondaparinux sodium is gained, platelet monitoring is recommended at baseline and at the end of treatment. This is especially important when follow-up therapy with heparin or low molecular weight heparin is considered.

Patients with Heparin Induced Thrombocytopenia

Fondaparinux should be used with caution in patients with a history of HIT. The efficacy and safety of fondaparinux have not been formally studied in HIT type II. Fondaparinux does not bind to platelet factor 4 and does not cross-react with sera from patients with HIT type II. However, rare spontaneous reports of HIT in patients treated with fondaparinux have been received. To date a causal association between treatment with fondaparinux and the occurrence of HIT has not been established.

Latex Allergy

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

Use in hepatic impairment

Since there is no evidence of metabolism or elimination by the liver, dosing adjustment of ARIXTRA is not necessary in patients with mild to moderate hepatic impairment. However, as for other medicinal products which interfere with blood coagulation, the use of ARIXTRA should be considered with caution because of an

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increased risk of bleeding due to a deficiency of coagulation factors in patients with severe hepatic impairment (see Section 4.2 Dose and method of administration).

Use in renal impairment

Fondaparinux is known to be mainly excreted by the kidney.

Prophylaxis of VTE and Treatment of Acute DVT and PE

ARIXTRA is contraindicated in severe renal impairment (creatinine clearance <30 mL/min) (see Section 4.2 Dose and method of administration and Section 4.3 Contraindications) and should be used with caution in patients with severe renal insufficiency (creatinine clearance < 30 mL/min) and moderate renal insufficiency (creatinine clearance 30 - 50 mL/min) as these patients may show delayed elimination of fondaparinux and are at increased risk of bleeding. Occurrences of major bleeding in patients receiving the recommended regimen in the treatment of DVT and PE with normal renal function, mild renal impairment, moderate renal impairment, and severe renal impairment have been found to be 0.4% (4/1132), 1.6% (12/733), 2.2% (7/318), and 7.3% (4/55), respectively.

Renal function should be assessed periodically in orthopaedic surgery patients receiving prophylactic therapy. ARIXTRA should be discontinued immediately in patients who develop severe renal impairment or labile renal function while on 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 may persist even longer in patients with renal impairment.

Treatment of UA/NSTEMI and STEMI

ARIXTRA is contraindicated in severe renal impairment (creatinine clearance <30 mL/min) (see Section 4.2 Dose and method of administration – Use in the elderly and Section 4.3 Contraindications)

Use in the elderly

The elderly population is at an increased risk of bleeding. Fondaparinux is known to be substantially excreted by the kidney. As renal function generally decreases with age, elderly patients may show reduced elimination and increased exposure of fondaparinux (see Section 5.2 Pharmacokinetic properties). ARIXTRA should be used with caution in elderly patients (see Section 4.2 Dose and method of administration).

Age is a recognised risk factor for venous thromboembolic events (VTE); in the prophylaxis studies, the VTE rate was uniformly lower in patients treated with ARIXTRA than with enoxaparin sodium across all age categories. The rate of bleeding appeared to be related to age, but was comparable with enoxaparin across all age categories. In the DVT and PE treatment studies, the risk of bleeding also increased with age.

Paediatric use

The safety and efficacy of ARIXTRA in patients under the age of 17 years has not been established.

Because the risk for bleeding during treatment with ARIXTRA is increased in adults who weigh <50kg, bleeding may be a particular concern in the paediatric population.

Effects on laboratory tests

Routine coagulation tests such as activated partial thromboplastin time (aPTT), activated clotting time (ACT), or prothrombin time (PT)/International Normalised Ratio (INR) and bleeding time or fibrinolytic activity are

not affected by the activity of fondaparinux. However, rare spontaneous reports of elevated aPTT have been received at the 2.5 mg dose.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Bleeding risk is increased with concomitant administration of fondaparinux and agents that may enhance the risk of haemorrhage (see Section 4.4 Special warnings and precautions for use). Agents which may enhance the risk of haemorrhage should be discontinued prior to initiation of ARIXTRA therapy. If co-administration is essential, close monitoring may be appropriate.

In clinical studies performed with ARIXTRA, the concomitant use of oral anticoagulants (warfarin), platelet inhibitors (aspirin), NSAIDs (piroxicam) and digoxin did not interact with the pharmacokinetics/pharmacodynamics of fondaparinux. In addition, fondaparinux neither influenced the INR activity of warfarin, nor the bleeding time under aspirin, or piroxicam treatment, nor the pharmacokinetics of digoxin at steady state.

If follow-up treatment is to be initiated with heparin or Low Molecular Weight Heparin (LMWH), the first injection should, as a general rule, be given one day after the last fondaparinux injection. If follow up treatment with a Vitamin K antagonist is required, treatment with fondaparinux should be continued until the target INR value has been reached.

If follow-up treatment is to be initiated with a direct oral anticoagulant (DOAC), start the DOAC <2 hours prior to the next scheduled dose of fondaparinux. Fondaparinux should be discontinued.

Since fondaparinux does not inhibit CYP450s (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4) in vitro, fondaparinux is not expected to interact with other medicinal products in vivo by inhibition of CYP-mediated metabolism.

Since fondaparinux does not bind significantly to plasma proteins other than ATIII, no interaction with other medicinal products by protein binding displacement are expected.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no human data on the effects of fondaparinux on male or female fertility. Fondaparinux did not affect the fertility and reproductive performance of male and female rats at SC doses of up to 10 mg/kg/day, resulting in exposures about twice the human AUC at the maximum recommended clinical dose (MRCD).

Use in pregnancy – Pregnancy Category C

Anticoagulant and thrombolytic agents can produce placental haemorrhage and subsequent prematurity and foetal loss. Fondaparinux crossed the placenta of rats and rabbits. Administration of fondaparinux during the period of organogenesis did not affect embryofoetal development of rats and rabbits at SC doses up to 10 mg/kg/day, with respective systemic exposures (plasma AUC) about 2 and 4 times the human clinical exposure. Limited data on exposed pregnancies are available for the 2.5 mg prophylaxis dose. For treatment doses, there are no adequate and well controlled studies of fondaparinux in pregnant women. Fondaparinux should be used during pregnancy only if clearly indicated as clinical experience in such conditions is limited.

Use in lactation

Fondaparinux was excreted in rat milk. No effects on pup survival and development were observed at doses up to 10 mg/kg/day administered to lactating rats, associated with maternal systemic exposure (plasma AUC) about twice the human clinical exposure at the MCRD.

It is not known whether fondaparinux is excreted in human milk. Because many medicinal products are excreted in human milk, breast-feeding is not recommended during treatment with fondaparinux.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effect on the ability to drive and to use machines have been performed.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical trial data

Prevention of VTE and treatment of DVT and PE

The data below reflects exposure in 6707 patients randomised to ARIXTRA in controlled trials of prophylaxis in hip fracture, hip replacement, or major knee surgeries, and in the treatment of DVT and PE, and in 1407 patients undergoing abdominal surgery.

Patients received ARIXTRA primarily in two large prophylaxis dose-response trials (n=989), four active-controlled prophylaxis trials with enoxaparin sodium (n=3616), a placebo-controlled extended prophylaxis trial (n=327), a dose-response trial in DVT treatment (n=111), an active-controlled trial with enoxaparin sodium in DVT treatment (n = 1091), an active-controlled trial with heparin in PE treatment (n=1092), and an active-controlled prophylaxis trial with dalteparin in abdominal surgery (n=1407) (see section 5.1 Pharmacodynamic properties - Clinical trials).

In the peri-operative prophylaxis randomised clinical trials of 7 ± 2 days, asymptomatic increases in AST and ALT levels greater than three times the upper limit of normal of the laboratory reference range have been reported in 1.7% and 2.6% of patients, respectively, during treatment with ARIXTRA 2.5 mg injection vs 3.2% and 3.9%, of patients, respectively, during treatment with enoxaparin sodium. Such elevations are fully reversible and are rarely associated with increases in bilirubin. In the extended prophylaxis clinical trial no significant differences in AST and ALT levels between ARIXTRA 2.5 mg injection and placebo treated patients were observed.

During ARIXTRA 2.5 mg prophylactic therapy in patients undergoing orthopaedic surgeries, as with other anti-thrombotics, bleeding was a common adverse reaction. The percentage of patients with adjudicated bleeding events are shown in Table 1.

Table 1: Summary of bleeding results from Peri-operative studies (first injection up to Day 11) and Extended Prophylaxis Study (randomisation to Day 24)
 (% of Patients)

SURGERY TYPE	Bleeding	Fondaparinux 2.5 mg daily	Enoxaparin
Knee Replacement (Pentamaks) ^a	Major bleeding ^b	2.1 ^d	0.2
	Minor bleeding ^c	2.7	3.7
Hip Replacement (Pentathlon 2000) ^a	Major bleeding	1.8	1.0
	Minor bleeding	1.5	2.1
(Ephesus) ^e	Major bleeding	4.1	2.8
	Minor bleeding	3.9	3.4
Hip Fracture (Penthifra) ^e	Major bleeding	2.2	2.3
	Minor bleeding	4.1	2.1
		Fondaparinux 2.5 mg daily	Placebo
Extended prophylaxis (Penthifra Plus)	Major bleeding ^b	2.4	0.6
	Minor bleeding ^c	1.5	0.6

^a Comparator was Enoxaparin 30 mg bid.

^b 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 ≥ 2 i.e. BI = drop in Hb pre-bleed minus post-bleed + number of units transfused. There were no fatal bleeds in the fondaparinux group, and one fatal bleed in the enoxaparin group.

^c Minor bleeding was clinically overt bleeding that was not major.

^d p value versus Enoxaparin is 0.0061.

^e Comparator was Enoxaparin 40 mg once daily.

The rates of bleeding events reported during the abdominal surgery clinical trial with ARIXTRA 2.5 mg injection are provided in Table 2 below.

Table 2: Summary of bleeding results from the Abdominal Surgery Study

Endpoint	Fondaparinux Sodium 2.5 mg SC once daily n = 1433	Dalteparin sodium 5000 IU SC once daily 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	38 (2.7%)	26 (1.8%)
non-surgical	9 (0.6%)	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 (e.g. intracranial, retroperitoneal, intra-ocular, pericardial, spinal or into adrenal gland), or leading to an intervention, and/or with a bleeding index (BI) ≥ 2 . (BI ≥ 2 calculated as [number of whole blood or packed red blood cell units transfused + [(pre-bleeding) – (post-bleeding)] hemoglobin (g/dL) values].)

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

A separate analysis of major bleeding according to the time of the first injection of ARIXTRA after surgical closure was performed. In this analysis the incidences of major bleeding were as follows: 3.4% (9/263) if the first injection was given < 6 hours and 2.8% (32/1139) if the first injection was performed ≥ 6 hours.

The rates of bleeding events reported during the DVT and PE clinical trials with the ARIXTRA injection treatment regimen are provided in Table 3 below.

Table 3: : Summary of bleeding episodes 1, 2 in DVT and PE Treatment Studies

	Fondaparinux Sodium Treatment Regimen	Enoxaparin Sodium 1 mg/kg SC q 12h	Heparin aPTT adjusted IV
	(N = 2294)	(N = 1101)	(N = 1092)
Major bleeding	28 (1.2%)	13 (1.2%)	12 (1.1%)
Minor bleeding	70 (3.1%)	33 (3.0%)	57 (5.2%)

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 haemoglobin 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.

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 4 below.

Other adverse events that occurred during treatment with ARIXTRA or dalteparin in the clinical trial with patients undergoing abdominal surgery and that occurred at a rate of at least 2% in any treatment group are provided in Table 5 below.

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 6 below.

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Table 4: Adverse Events Occurring in 2% of ARIXTRA, Enoxaparin Sodium or Placebo Treated Patients Regardless of Relationship to Study Drug Across Randomised, Controlled, Hip Fracture Surgery, Hip Replacement Surgery or Knee Replacement Surgery Studies

Adverse events	Peri-Operative Prophylaxis (Day 1 to Day 7±1 post-surgery)		Extended Prophylaxis (Day 8 to Day 28±2 post-surgery)	
	Fondaparinux Sodium 2.5 mg SC once daily	Enoxaparin Sodium ¹	Fondaparinux Sodium 2.5 mg SC once daily	Placebo SC once daily
	N = 3616	N = 3956	N = 327	N = 329
Anaemia	707 (19.6%)	670 (16.9%)	5 (1.5%)	4 (1.2%)
Fever	491 (13.6%)	610 (15.4%)	1 (0.3%)	4 (1.2%)
Nausea	409 (11.3%)	484 (12.2%)	1 (0.3%)	4 (1.2%)
Oedema	313 (8.7%)	348 (8.8%)	3 (0.9%)	2 (0.6%)
Constipation	309 (8.5%)	416 (10.5%)	6 (1.8%)	7 (2.1%)
Rash	273 (7.5%)	329 (8.3%)	2 (0.6%)	4 (1.2%)
Vomiting	212 (5.9%)	236 (6.0%)	2 (0.6%)	4 (1.2%)
Insomnia	179 (5.0%)	214 (5.4%)	3 (0.9%)	1 (0.3%)
Wound drainage increased	161 (4.5%)	184 (4.7%)	2 (0.6%)	0 (0.0%)
Hypokalemia	152 (4.2%)	164 (4.1%)	0 (0.0%)	0 (0.0%)
Urinary tract infection	136 (3.8%)	135 (3.4%)	13 (4.0%)	13 (4.0%)
Dizziness	131 (3.6%)	165 (4.2%)	2 (0.6%)	0 (0.0%)
Purpura	128 (3.5%)	137 (3.5%)	0 (0.0%)	0 (0.0%)
Hypotension	126 (3.5%)	125 (3.2%)	1 (0.3%)	0 (0.0%)

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Adverse events	Peri-Operative Prophylaxis (Day 1 to Day 7±1 post-surgery)		Extended Prophylaxis (Day 8 to Day 28±2 post-surgery)	
	Fondaparinux Sodium 2.5 mg SC once daily	Enoxaparin Sodium ¹	Fondaparinux Sodium 2.5 mg SC once daily	Placebo SC once daily
Confusion	113 (3.1%)	132 (3.3%)	4 (1.2%)	1 (0.3%)
Bullous eruption ²	112 (3.1%)	102 (2.6%)	0 (0.0%)	1 (0.3%)
Urinary retention	106 (2.9%)	117 (3.0%)	0 (0.0%)	1 (0.3%)
Haematoma	103 (2.8%)	109 (2.8%)	7 (2.1%)	1 (0.3%)
Diarrhoea	90 (2.5%)	102 (2.6%)	6 (1.8%)	8 (2.4%)
Dyspepsia	87 (2.4%)	102 (2.6%)	1 (0.3%)	2 (0.6%)
Post-operative haemorrhage	85 (2.4%)	69 (1.7%)	2 (0.6%)	2 (0.6%)
Headache	72 (2.0%)	97 (2.5%)	0 (0.0%)	2 (0.6%)
Pain	62 (1.7%)	101 (2.6%)	0 (0.0%)	0 (0.0%)
Surgical site reaction	29 (0.8%)	41 (1.0%)	5 (1.5%)	8 (2.4%)

1. Enoxaparin sodium dosing regimen: 30 mg twice daily or 40 mg once daily.

2. Localised blister coded as bullous eruption.

Table 5: Adverse Events Occurring in > 2% of ARIXTRA or Dalteparin Sodium Treated Patients Undergoing Abdominal Surgery Regardless of Relationship to Study Drug

Adverse Events	Fondaparinux sodium 2.5 mg SC once daily	Dalteparin sodium 5000 IU SC once daily
	N = 1433	N = 1425
Post-operative wound infection	70 (4.9%)	69 (4.8%)
Post-operative haemorrhage	61 (4.3%)	42 (2.9%)
Fever	53 (3.7%)	54 (3.8%)

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Adverse Events	Fondaparinux sodium 2.5 mg SC once daily	Dalteparin sodium 5000 IU SC once daily
Surgical site reaction	46 (3.2%)	40 (2.8%)
Anaemia	35 (2.4%)	26 (1.8%)
Hypertension	35 (2.4%)	41 (2.9%)
Pneumonia	33 (2.3%)	23 (1.6%)
Vomiting	31 (2.2%)	26 (1.8%)

Table 6: Adverse Events Occurring in 2% of ARIXTRA, Enoxaparin Sodium or Heparin Treated Patients Regardless of Relationship to Study Drug Across VTE Treatment Studies

Adverse events	Fondaparinux Sodium Treatment Regimen	Enoxaparin Sodium 1 mg/kg SC q 12h	Heparin aPTT adjusted IV
	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%)
Diarrhoea	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%)

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Adverse events	Fondaparinux Sodium Treatment Regimen	Enoxaparin Sodium 1 mg/kg SC q 12h	Heparin aPTT adjusted IV
Prothrombin decreased	30 (1.3%)	3 (0.3%)	34 (3.1%)
Anaemia	28 (1.2%)	3 (0.3%)	23 (2.1%)
Vomiting	26 (1.1%)	14 (1.3%)	27 (2.5%)
Hypokalaemia	25 (1.1%)	2 (0.2%)	23 (2.1%)
Bruising	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 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% include the following: thrombocytopenia, thrombocythemia, abnormal platelets, coagulation disorder, pruritus, hepatic enzymes increased, hepatic function abnormal and wound secretion. Adverse reactions occurring at a rate of less than 0.1% include somnolence, vertigo, dyspnea, gastritis, bilirubinemia, fatigue, flushing and syncope.

Other adverse reactions that occurred during treatment with ARIXTRA in the DVT and PE treatment clinical trials and that occurred at a rate of less than 1% include thrombocytopenia, hepatic enzymes increased and hepatic function abnormal. Adverse reactions occurring at a rate of less than 0.1% include thrombocythemia, pruritis and injection site.

UA/NSTEMI and STEMI ACS

The safety of Arixtra 2.5 mg has been evaluated in 10,057 patients undergoing treatment of UA or NSTEMI ACS and 6,036 patients undergoing treatment of STEMI ACS. The safety of Arixtra 2.5 mg was further evaluated in 3,235 high-risk patients for the treatment of UA/NSTEMI who underwent coronary angiography and PCI with adjunctive UFH if indicated.

The adverse event profile reported in the ACS program is consistent with the adverse drug reactions identified for VTE prophylaxis.

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Bleeding was a commonly reported event in patients with UA/NSTEMI and STEMI. The incidence of adjudicated major bleeding was 2.1% (fondaparinux) versus 4.1% (enoxaparin) up to and including Day 9 in the phase III UA/NSTEMI study (Table 7).

Table 7: Bleeding Events Occurring in UA/NSTEMI Patients Treated With Fondaparinux or Enoxaparin (OASIS 5)

Any Bleeding Event to Day 9 (N(%))	Fondaparinux N=9,979	Enoxaparin N=9,969
Any Bleeding (Major or Minor Bleeding)	314 (3.1%)	721 (7.2%)
Minor bleeding	205 (2.1%)	410 (4.1%)
Minor bleeding	115 (1.2%)	320 (3.2%)
TIMI severe haemorrhage	148 (1.5%)	260 (2.6%)

The incidence of adjudicated severe haemorrhage by modified thrombolysis in myocardial infarction (TIMI) criteria was 1.1% (fondaparinux) versus 1.4% (control [UFH/placebo]) up to and including Day 9 in the Phase III STEMI study (Table 8).

Table 8: Bleeding Events Occurring in STEMI Patients Treated With Fondaparinux or Enoxaparin (OASIS 6)

Any Bleeding Event to Day 9 (N(%))	Overall		Stratum 1		Stratum 2	
	Fondaparinux N=5,954	Control N=5,947	Fondaparinux N=2,808	Placebo N=2,818	Fondaparinux N=3,146	UFH N=3,129
TIMI severe haemorrhage	64 (1.1%)	83 (1.4%)	28 (1.0%)	46 (1.6%)	36 (1.1%)	37 (1.2%)
Major Bleeding	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%)

The risk of peri-PCI major bleeding when ARIXTRA was used in conjunction with UFH was low and comparable to that observed in the Phase III UA/NSTEMI study (see Section 5.1 Pharmacodynamic properties – Clinical trials, Table 18).

In the Phase III UA/NSTEMI study, the most commonly reported non-bleeding adverse events (reported in at least 1% of subjects on fondaparinux) were headache, chest pain and atrial fibrillation (Table 9).

Table 9: Adverse Events Occurring in 1% of UA/NSTEMI Patients Treated With Fondaparinux or Enoxaparin (OASIS 5)

Adverse Events (N(%))	Fondaparinux N=9,979	Enoxaparin N=9,969
Any Adverse Event	2,426 (24%)	2,785 (28%)
Headache	227 (2%)	226 (2%)
Atrial fibrillation	103 (1%)	124 (1%)
Pyrexia	96 (<1%)	110 (1%)
Chest pain	148 (1%)	147 (1%)

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In the Phase III study in STEMI patients, the most commonly reported non-bleeding adverse events (reported in at least 1% of subjects on fondaparinux) were atrial fibrillation, pyrexia, chest pain, headache, ventricular tachycardia, vomiting, and hypotension (Table 10).

Table 10: Adverse Events Occurring in ≥ 1% of STEMI Patients Treated With Fondaparinux or Enoxaparin (OASIS 6)

Adverse Events (N(%))	Overall		Stratum 1		Stratum 2	
	Fondaparinux N=5,954	Control N=5,947	Fondaparinux N=2,808	Placebo N=2,818	Fondaparinux N=3,146	UFH N=3,129
Any Adverse Event	1,933 (32%)	1,959 (33%)	922 (33%)	954 (34%)	1,011 (32%)	1,005 (32%)
headache	105 (2%)	118 (2%)	60 (2%)	63 (2%)	45 (1%)	55 (2%)
atrial fibrillation	164 (3%)	126 (2%)	69 (2%)	57 (2%)	95 (3%)	69 (2%)
pyrexia	189 (3%)	200 (3%)	119 (4%)	125 (4%)	70 (2%)	75 (2%)
chest pain	108 (2%)	79 (1%)	50 (2%)	42 (1%)	58 (2%)	37 (1%)
hypotension	75 (1%)	72 (1%)	36 (1%)	35 (1%)	39 (1%)	37 (1%)
vomiting	74 (1%)	74 (1%)	47 (2%)	42 (1%)	27 (1%)	32 (1%)
ventricular tachycardia	76 (1%)	81 (1%)	26 (<1%)	29 (1%)	50 (2%)	52 (2%)
urinary tract infection (not otherwise specified)	48 (<1%)	52 (<1%)	24 (<1%)	18 (<1%)	24 (<1%)	34 (1%)

Catheter-related thrombosis

The incidence of adjudicated catheter thrombosis in STEMI patients who underwent PCI in the phase III OASIS 6 study was 1.1% for the fondaparinux group and 0% for the UFH control group.

The incidence of adjudicated catheter thrombus in UA/NSTEMI patients who underwent PCI in the phase III OASIS 5 study was 1.0% for the fondaparinux group and 0.3% for the enoxaparin group.

In high-risk UA/NSTEMI patients who underwent PCI with adjunctive UFH in the OASIS 8/FUTURA study, the incidence of confirmed catheter-related thrombosis was low and less than that previously observed in the phase III study (0.5% for low dose UFH and 0.1% for high dose UFH). No new safety signals with the use of fondaparinux in conjunction with UFH during PCI were observed.

See also Section 4.4 Special warnings and precautions for use, PCI and risk of guiding catheter thrombus.

Haematological – intracranial haemorrhage and retroperitoneal bleeding

In post-marketing experience, as in clinical trials, rare cases of intracranial/intracerebral or retroperitoneal bleeding have been reported.

Immune system disorders - angioedema, anaphylactoid/anaphylactic disorders

In clinical studies or in post-marketing experience, rare cases of allergic reaction (including very rare reports of angioedema, anaphylactoid/anaphylactic reaction) have been reported.

Note

very common	≥	1/10 (10%)
common	≥	1/100 and < 1/10 (1% and <10%)
uncommon	≥	1/1000 and < 1/100 (0.1% and <1.0%)
rare	≥	1/10,000 and < 1/1000 (0.01% and < 0.1%)
very rare	<	1/10,000 (< 0.01%)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

As with any anti-thrombotic agent, ARIXTRA doses above the recommended regimen may lead to an increased risk of bleeding.

There is no antidote for ARIXTRA. Overdosage associated *Overdosage associated with bleeding complications should lead to treatment discontinuation and search for the primary cause. Initiation of appropriate therapy which may include surgical haemostasis, blood replacements, fresh plasma transfusion, plasmapheresis should be considered.*

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Fondaparinux is a synthetic and specific inhibitor of activated Factor X (Xa) with no animal sourced components. The anti-thrombotic activity of fondaparinux is the result of antithrombin III (ATIII) mediated selective inhibition of Factor Xa. By binding selectively to ATIII, fondaparinux potentiates (about 300 times) the innate neutralisation of Factor Xa by antithrombin. Neutralisation of Factor Xa interrupts the blood coagulation cascade and inhibits both thrombin formation and thrombus development.

Fondaparinux does not inactivate thrombin (activated Factor II) and has no effects on platelet aggregation. It does not cross-react with sera from patients with heparin-induced thrombocytopenia. At the recommended dose, it does not affect fibrinolytic activity or bleeding time.

At equivalent anti-thrombotic doses, an experimental bleeding model in rats demonstrates that fondaparinux induces less bleeding than unfractionated heparin.

Clinical trials

Over 21,800 patients (age 17 to 101 years; body weight 30 to 226 kg) have been studied in controlled Phase II and III clinical studies of fondaparinux.

Prevention of VTE

In a double blind dose-response clinical study of fondaparinux (0.75 to 8 mg once daily) in patients undergoing hip replacement surgery, a statistically significant dose response ($p = 0.003$) for prevention of VTE was demonstrated. This dose effect relationship was confirmed in a second dose-response study performed in patients undergoing knee replacement. Based on these studies, a 2.5 mg once daily dose of fondaparinux was selected for the Phase III clinical development program.

The efficacy of fondaparinux 2.5 mg in preventing VTE was confirmed in four Phase III studies in patients undergoing major orthopaedic surgery of the lower limbs: PENTHIFRA (hip fracture), PENTAMAKS (knee replacement), PENTATHLON 2000 and EPHEBUS (hip replacement).

The trials included sufficient numbers of patients to demonstrate the superiority of fondaparinux versus enoxaparin. Enoxaparin was administered according to two different regimens; the 40 mg daily regimen approved in Australia and Europe and the 30 mg bd regimen approved in North America.

The efficacy of fondaparinux 2.5 mg for extended prevention of VTE was confirmed in the PENTHIFRA PLUS study (Extended prophylaxis in hip fracture surgery).

The efficacy of fondaparinux 2.5 mg in preventing VTE in patients undergoing abdominal surgery was confirmed in the PEGASUS study.

Prevention of Venous Thromboembolic Events in Hip Fracture Surgery - PENTHIFRA

A randomised, double-blind clinical trial compared the efficacy of a subcutaneous once daily injection of fondaparinux 2.5 mg to enoxaparin 40 mg during 7*2 days in patients undergoing hip fracture surgery. ARIXTRA was initiated after surgery in 88% of patients (mean 6 hrs) and enoxaparin sodium was initiated after surgery in 74% of patients (mean 18 hrs). The efficacy data are provided in Table 11.

Table 11: Efficacy of Fondaparinux injection in hip fracture surgery

Adjudicated Endpoint	Fondaparinux 2.5 mg once daily^a	Enoxaparin 40 mg once daily^b
VTE (primary analysis)	52/626 (8.3%) [6.3, 10.8] ^c p < 0.0001	119/624 (19.1%) [16.1, 22.4]
DVT	49/624 (7.9%) [5.9, 10.2] p < 0.001	117/623 (18.8%) [15.8, 22.1]
Proximal DVT	6/650 (0.9%) [0.3, 2.0] p = 0.001	28/646 (4.3%) [2.9, 6.2]
Pulmonary embolism	3/831 (0.4%) [0.1, 1.1] p = NS	3/840 (0.4%) [0.1, 1.0]

^a Fondaparinux randomised patients were to receive the first 2.5 mg injection 12 hours before the operation when surgery was delayed by more than 24 hours after admission except in case of spinal anaesthesia.

^b Enoxaparin randomised patients were to receive the first 40 mg injection 12 hours before the operation except in case of spinal anaesthesia (at the discretion of the investigator) or surgery performed within less than 12 hours after admission.

^c numbers in square brackets indicate 95% confidence interval.

Extended Prevention of Venous Thromboembolic Events in Hip Fracture Surgery – PENTHIFRA PLUS

A randomised double blind clinical trial involving 737 patients examined the additional effect of extending prophylaxis for VTE from 7 days to 28-31 days. After 7*1 days of treatment with ARIXTRA 2.5 mg once daily following hip fracture surgery, patients were randomised to receive ARIXTRA 2.5 mg once daily (n=327) or placebo (n=329) for an additional 21*2 days. After 28 days of treatment, fondaparinux provided a statistically significant reduction (p < 0.001) of 96% in the rate of VTE compared to placebo. Fondaparinux also provided a statistically significant 89% reduction in the rate of symptomatic VTE, which was defined as DVT, fatal and non-fatal PE.

Table 12: Efficacy of ARIXTRA injection in Extended Prophylaxis of Thromboembolic events following hip fracture surgery

Adjudicated Endpoint	Extended Prophylaxis (Day 8 to Day 28 +/- 2 post-surgery) ¹	
	Fondaparinux 2.5 mg once daily	Placebo SC once daily
All randomised treated hip fracture surgery patients	N = 326	N = 330
VTE ²	3/208 (1.4%) [0.3, 4.2] p < 0.001	77/220 (35%) [28.7, 41.7]
All DVT	3/208 (1.4%) [0.3, 4.2] p < 0.001	74/218 (33.9%) [27.7, 40.6]
Proximal DVT	2/221 (0.9%) [0.1, 3.2] p < 0.001	35/222 (15.8%) [11.2, 21.2]
Symptomatic VTE (all)	1/326 (0.3%) [0.0, 1.7] p = 0.021	9/330 (2.7%) [1.3, 5.1]

¹ Evaluable patients were those who were treated in the post-randomisation period, with an adequate efficacy assessment up to Day 24 following randomisation

² VTE was a composite of documented DVT and/or documented symptomatic PE reported up to Day 24 following randomisation.

Major bleeding, all at surgical sites, was observed in 8 patients (2.4%) treated with ARIXTRA 2.5 mg compared to 2 (0.6%) with placebo (p=0.063). Permanent premature treatment cessation was observed in 2 of these patients in the ARIXTRA group and in 1 patient in the placebo group. In each group, two of these major bleeding episodes (0.6%) led to surgical re-intervention. Death occurred in 5 randomised patients (1.5%) treated with ARIXTRA 2.5 mg compared to 7 (2.1%) with placebo. The 2 excess deaths with placebo were due to PE.

Prevention of Venous Thromboembolic Events in Major Knee Surgery - PENTAMAKS

A randomised, double-blind clinical trial compared the efficacy of a subcutaneous once daily injection of fondaparinux 2.5 mg to enoxaparin 30 mg b.i.d. during 7*2 days in patients undergoing major knee surgery. 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. The efficacy data are provided in Table 13.

Table 13: Efficacy of Fondaparinux injection in major knee surgery

Adjudicated Endpoint	Fondaparinux 2.5 mg once daily ^a	Enoxaparin 30 mg b.i.d. ^{a, b}
VTE (primary analysis)	45/361 (12.5%) [9.2, 16.3] p < 0.001	101/363 (27.8%) [23.3, 32.7]
DVT	45/361(12.5%) [9.2, 16.3] p < 0.001	98/361(27.1%) [22.6, 32.0]

Adjudicated Endpoint	Fondaparinux 2.5 mg once daily ^a	Enoxaparin 30 mg b.i.d. ^{a, b}
Proximal DVT	9/368 (2.4%) [1.1, 4.6] p = NS	20/372 (5.4%) [3.3, 8.2]
Pulmonary embolism	1/517 (0.2%) [0.0, 1.1] p = NS	4/517 (0.8%) [0.2, 2.0]

^a First injection was to be given post-operatively.

^b This dosage schedule is approved in North America but not in Australia.

Prevention of Venous Thromboembolic Events in Hip Replacement - PENTATHLON 2000 and EPHEBUS

In two randomised, double-blind, controlled clinical trials, the efficacy of a subcutaneous once daily injection of fondaparinux 2.5 mg was compared to either 30 mg b.i.d. or to 40 mg once daily subcutaneous injection of enoxaparin, during 7*2 days, in patients undergoing hip replacement surgery, respectively. In Pentathlon 2000, 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 Ephesus, 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 hours. The efficacy data are provided in Table 14.

Table 14: Efficacy of Fondaparinux Injection in hip replacement surgery

Adjudicated Endpoint	Pentathlon 2000		Ephesus	
	Fondaparinux 2.5 mg once daily ^a	Enoxaparin 30 mg b.i.d. ^{a, c}	Fondaparinux 2.5 mg once daily ^a	Enoxaparin 40 mg once daily ^b
VTE (primary analysis)	48/787 (6.1%) [4.5, 8.0] p = NS	66/797 (8.3%) [6.5, 10.4]	37/908 (4.1%) [2.9, 5.6] p < 0.0001	85/919 (9.2%) [7.5, 11.3]
DVT	44/784 (5.6%) [4.1, 7.5] p = 0.047	65/796 (8.2%) [6.1, 10.3]	36/908 (4.0%) [2.8, 5.4] p < 0.0001	83/918 (9.0%) [7.3, 11.1]
proximal DVT	14/816 (1.7%) [0.9, 2.9] p = NS	10/830 (1.2%) [0.6, 2.2]	6/922 (0.7%) [0.2, 1.4] p = 0.0021	23/927 (2.5%) [1.6, 3.7]
Pulmonary embolism	5/1126 (0.4%) [0.1, 1.0] p = NS	1/1128 (0.1%) [0.0, 0.5]	2/1129 (0.2%) [0.0, 0.6] p = NS	2/1123 (0.2%) [0.0, 0.6]

^a First injection was to be given post-operatively.

^b first injection was to be given 12 hours before operation except in case of spinal anaesthesia (at the discretion of the investigator).

^c This dosage schedule is approved in North America but not in Australia.

Prevention of Venous Thromboembolic Events in patients undergoing abdominal surgery at risk of thromboembolic complications – PEGASUS

In a randomised, double-blind, clinical trial in patients undergoing abdominal surgery, fondaparinux 2.5 mg SC once daily started postoperatively was compared to dalteparin sodium 5000 IU SC once daily, with one 2500 IU SC preoperative injection and a 2500 IU SC first postoperative injection. A total of 2927 patients were randomised and 2858 were treated. Study treatment was continued for 7 ± 2 days. The efficacy data are provided in Table 15 below.

Table 15: Efficacy of Fondaparinux Injection in abdominal surgery patients

	Fondaparinux 2.5 mg once daily	Dalteparin Sodium 5000 IU	Odds Ratio Reduction [CI]*
Primary efficacy outcome			
VTE	47/1027 (4.6%)	62/1021 (6.1%)	NS
Component of the primary efficacy outcome (secondary analysis)			
Any DVT	43/1024 (4.2%)	59/1018 (5.8%)	-28.8% [-52.4, -6.6]
Any proximal DVT	5/1076 (0.5%)	5/1077 (0.5%)	NS
Distal DVT only	40/1025 (3.9%)	54/1022 (5.3%)	--
Symptomatic VTE	6/1465 (0.4%)	5/1462 (0.3%)	--
Symptomatic DVT	2	2	--
Non-Fatal PE	2	0	--
Fatal PE	3	3	--

* The Odds Ratio Reduction is only presented for pre-specified analyses
 NS - not statistically significant

The difference in the rate of VTE observed between patients taking fondaparinux and those taking dalteparin (4.6% and 6.1%) was not statistically significant. The PEGASUS trial indicates that fondaparinux is non-inferior to dalteparin in the prevention of DVT after abdominal surgery.

Treatment of Deep Vein Thrombosis

In a randomised, double-blind, clinical trial in patients with a confirmed diagnosis of acute symptomatic DVT, ARIXTRA 5 mg (< 50 kg), 7.5 mg (50 –100 kg) or 10 mg (>100 kg) SC once daily was compared to enoxaparin sodium 1 mg/kg SC every 12 hours in both hospitalised and non-hospitalised patients. Outpatient and home treatment with ARIXTRA was permitted, and approximately 32% of patients were discharged home from the hospital while receiving fondaparinux therapy. A total of 2205 patients were randomised and 2192 were treated. Patients ranged in age from 18–95 years (mean age 61 years) with 53% men and 47% women. 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. The efficacy data are provided in Table 16 below.

Table 16: Efficacy of ARIXTRA Injection in the Treatment of Deep Vein Thrombosis

Adjudicated Endpoint	Fondaparinux Sodium ¹ 5, 7.5 or 10 mg SC once daily	Enoxaparin Sodium ¹ 1 mg/kg SC q 12h
ALL RANDOMISED PATIENTS	N = 1098	N = 1107
Total VTE ²	43 (3.9%) [-1.8, 1.5] ³	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. 95% confidence interval for the treatment difference		

Treatment of Pulmonary Embolism

In a randomised, open-label, clinical trial in patients with a confirmed diagnosis of acute symptomatic PE, with or without DVT, ARIXTRA 5 mg (< 50 kg), 7.5 mg (50–100 kg) or 10 mg (>100 kg) SC once daily was compared to heparin IV bolus (5000 USP units) followed by a continuous IV infusion adjusted to maintain 1.5–2.5 times the 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 2213 patients were randomised and 2184 were treated. Patients ranged in age from 18–97 years (mean age 62 years) with 44% men and 56% women. 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. The efficacy data are provided in Table 17 below.

Table 17:

Adjudicated Endpoint	Fondaparinux Sodium ¹ 5, 7.5 or 10 mg SC once daily	Heparin ¹ aPTT adjusted IV
ALL RANDOMISED PATIENTS	N = 1103	N = 1110
Total VTE ²	42 ³ (3.8%) [-3.0, 0.5%]	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. 95% confidence interval for the treatment difference		

Treatment of unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI)

OASIS 5 was a double-blind, randomised, non-inferiority study with fondaparinux 2.5 mg subcutaneously once daily versus enoxaparin 1 mg/kg subcutaneously twice daily in approximately 20,000 patients with UA/NSTEMI. All patients received standard medical treatment for UA/NSTEMI, with 34% of patients undergoing PCI and 9% undergoing coronary artery bypass graft (CABG). The mean treatment duration was 5.5 days in the fondaparinux group and 5.2 days in the enoxaparin group. If PCI was performed, patients received either intravenous fondaparinux (fondaparinux patients) or weight adjusted intravenous unfractionated heparin (UFH, enoxaparin patients) as adjunctive therapy, dependent on the timing of the last subcutaneous dose and planned use of GP IIb/IIIa inhibitor. The mean age of the patients was 67 years, and approximately 60% were at least 65 years old. 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 impairment, respectively. Patients with serum creatinine ≥ 265 $\mu\text{mol/L}$ were excluded from the study.

The primary adjudicated endpoint was a composite of death, myocardial infarction (MI) and refractory ischaemia (RI) within 9 days of randomisation. Of the patients in the fondaparinux group, 5.8% experienced an event by Day 9 compared to 5.7% for enoxaparin-treated patients (hazard ratio 1.01, 95% CI, 0.90, 1.13, one-sided non-inferiority p value = 0.003).

By Day 30, the incidence of all cause mortality was significantly reduced from 3.5% on enoxaparin to 2.9% on fondaparinux (hazard ratio 0.83, 95% CI, 0.71; 0.97,). The effects on the incidence of MI and RI were not statistically different between the fondaparinux and enoxaparin treatment groups.

At Day 9 the incidence of major bleeding on fondaparinux and enoxaparin was 2.1% and 4.1%, respectively (hazard ratio 0.52, 95% CI, 0.44; 0.61,).

The efficacy findings and results on major bleeding were consistent across prespecified subgroups such as elderly, renally impaired patients, type of concomitant platelet aggregation inhibitors (aspirin, thienopyridines or GP IIb/IIIa inhibitors).

In the subgroup of patients treated with fondaparinux or enoxaparin who underwent PCI, 8.8% and 8.2% of patients respectively, experience death/MI/RI within 9 days of randomisation (hazard ratio 1.08, 95% CI, 0.92;1.27). In this subgroup, the incidence of major bleeding on fondaparinux and enoxaparin at Day 9 was 2.2% and 5.0% respectively (hazard ratio 0.43, 95% CI, 0.33;0.57). In subjects undergoing PCI the incidence of adjudicated guiding catheter thrombus was 1.0% vs. 0.3% in fondaparinux vs. enoxaparin subjects, respectively.

Treatment of unstable angina (UA) or non-ST segment elevation myocardial infarction (NSTEMI) in patients who underwent subsequent PCI with adjunctive UFH

In a study of 3,235 high-risk UA/NSTEMI patients scheduled for angiography and treated with open-label fondaparinux (OASIS 8/FUTURA), 2,026 patients indicated for PCI were randomised to receive one of two double-blind dose regimens of adjunctive UFH. The remaining 1209 patients were not indicated for PCI and were not randomised to receive UFH.

All enrolled patients received fondaparinux 2.5 mg subcutaneously, once daily for up to 8 days, or until hospital discharge. Randomised patients received either "low dose" UFH regimen (50 U/kg irrespective of planned GPIIb/IIIa use; non ACT guided) or "standard dose" UFH regimen (no GPIIb/IIIa use: 85 U/kg, ACT guided; planned GPIIb/IIIa use: 60 U/kg, ACT guided) immediately prior to the start of the PCI.

The baseline characteristics and duration of fondaparinux treatment were comparable in both UFH groups. In subjects randomised to the “standard dose UFH” or the “low dose UFH” regimen the median dose of UFH was 85 U/kg and 50 U/kg, respectively.

The primary outcome was a composite of peri-PCI (defined as time of randomisation up to 48 hours post-PCI) adjudicated major or minor bleeding, or major vascular access site complications.

Table 18: Incidence of peri-PCI major or minor bleeding or major vascular site complications during index PCI

Outcomes	Incidence		Odds Ratio ¹ (95%CI)
	Low Dose UFH N = 1024	Standard Dose UFH N = 1002	
Primary Peri-PCI major or minor bleeding, or major vascular access site complications	4.7%	5.8%	0.80 (0.54, 1.19)
Secondary			
Peri-PCI major bleeding	1.4%	1.2%	1.14 (0.53, 2.49)
Peri-PCI minor bleeding	0.7%	1.7%	0.40 (0.16, 0.97)
Major vascular access site complications	3.2%	4.3%	0.74 (0.47, 1.18)
Peri-PCI major bleeding or death, MI or TVR at Day 30	5.8%	3.9%	1.51 (1.0, 2.28)
Death, MI or TVR at Day 30	4.5%	2.9%	1.58 (0.98, 2.53)

¹Odds ratio: Low Dose/Standard Dose

²p value is 0.267

Note: MI - myocardial infarction. TVR - target vessel revascularization

The incidences of adjudicated guiding catheter thrombus were 0.1% (1/1002) and 0.5% (5/1024), in patients randomised to “standard dose” and “low dose” UFH respectively during PCI. Four (0.3%) non-randomised patients experienced thrombus in the diagnostic catheter during coronary angiography. Of the 3,235 patients enrolled in the trial, twelve (0.37%) patients in total experienced thrombus in the arterial sheath, of these 7 cases were reported during angiography and 5 cases were reported during PCI.

Treatment of ST segment elevation myocardial infarction (STEMI)

OASIS 6 was a double blind, randomised study assessing the safety and efficacy of fondaparinux 2.5 mg once daily, versus usual care (placebo (47%) or UFH (53%)) in approximately 12,000 patients with STEMI. All patients received standard treatments for STEMI, including primary PCI (31%), thrombolytics (45%) or no reperfusion (24%). Of the patients treated with a thrombolytic, 84% were treated with a non-fibrin specific agent (primarily streptokinase). The mean treatment duration was 6.2 days on fondaparinux. The mean age of the patients was 61 years, and approximately 40% were at least 65 years old. 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 impairment, respectively. Patients with serum creatinine ≥ 265 $\mu\text{mol/L}$ were excluded from the study.

The primary adjudicated endpoint was a composite of death and recurrent MI (re-MI) within 30 days of randomisation. In the population undergoing no reperfusion (i.e. patients not undergoing primary PCI or thrombolysis), the incidence of death/re-MI at Day 30 was significantly reduced from 15% for the control group to 12.1% for the fondaparinux group (hazard ratio 0.79, 95% CI, 0.65;0.97).

The incidence of all cause mortality at Day 30 was also significantly reduced from 8.9% for the control group to 7.8% in the fondaparinux group (hazard ratio 0.87, 95% CI, 0.77;0.98). The difference in mortality was statistically significant in stratum 1 (placebo comparator) but not in stratum 2 (UFH comparator). The mortality benefit shown in the fondaparinux group was maintained until the end of follow-up at Day 180.

By Day 9, 1.1% of patients treated with fondaparinux and 1.4% of control patients experienced a severe haemorrhage. In patients initially not reperfused, the incidence of severe haemorrhage was 1.2% for fondaparinux vs 1.5% for controls. At day 30, the incidence of severe haemorrhage was 0.7% for fondaparinux vs 0.8% for placebo, and 1.7% for fondaparinux vs 2.1% for UFH. For patients receiving primary PCI, the incidence of severe haemorrhage was 1.0% for fondaparinux and 0.4% for controls.

In subjects undergoing primary PCI the incidence of adjudicated guiding catheter thrombus was 1.2% vs 0% in fondaparinux vs. control subjects, respectively. The efficacy findings and results on severe haemorrhage were consistent across prespecified subgroups such as elderly, renally impaired patients, type of concomitant platelet aggregation inhibitors (aspirin, thienopyridines).

Use in Paediatric Patients

Safety and effectiveness of fondaparinux in paediatric patients have not been established.

In an open-label study, 24 paediatric patients diagnosed with venous thrombosis at study entry (with the exception of one patient who had an arterial thrombosis) were administered fondaparinux. No patient had heparin induced thrombocytopenia (HIT) although one patient had a medical history of HIT following extracorporeal circulation membrane oxygenation. The majority of patients were Hispanic (67%) and 58% were male. Ten patients were 1 to 5 years of age (weight range 8 to 20 kg), 7 patients were 6 to 12 years of age (weight range 17 to 47 kg), and 7 patients were 13 to ≥ 18 years of age (weight range 47 to 130 kg). Fondaparinux was administered at an initial dose of 0.1 mg/kg subcutaneously once daily. Dosing was adjusted to achieve peak (4 hour post dosing) fondaparinux sodium concentrations (0.5 <1 mg/L). One patient received concomitant warfarin and fondaparinux for 3 days during the study. The median duration of treatment in this study was 3.5 days.

The purpose of this study was to evaluate the pharmacokinetics and safety of fondaparinux in a paediatric population. The majority of patients (88%) achieved target fondaparinux concentrations after the first dose of fondaparinux. Population pharmacokinetic modelling (based on combining paediatric data with the complete data in healthy adult males) and simulations demonstrated that the 0.1 mg/kg once daily dose resulted in fondaparinux concentrations that were similar to those observed in adults receiving fondaparinux for the treatment of DVT or PE. There were no apparent differences in achieving the target fondaparinux concentration range between age groups. Note that data in the paediatric study were sparse, necessitating the use of a population PK model.

Two patients had reports of bleeding during the study. One experienced hypertensive encephalopathy accompanied by intracranial bleeding on day 5 of therapy resulting in discontinuation of fondaparinux. Minor gastrointestinal bleeding was reported in another patient on day 5 of therapy which resulted in temporary discontinuation of fondaparinux.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

After subcutaneous dosing, fondaparinux is completely and rapidly absorbed, the absolute bioavailability being 100%. Following a single subcutaneous injection of 2.5 mg of fondaparinux, 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.

Mean (SD) pharmacokinetic parameters of fondaparinux following a single subcutaneous injection of ARIXTRA 2.5 mg in young healthy subjects are provided in Table 19 below:

Table 19: Mean (SD) Pharmacokinetic Parameters

T_{max} (h)	C_{max} (mg/L)	AUC _{0-inf} (mg.h/L)	$T_{1/2}$ (h)	Plasma Clearance (mL/min)	Distribution volume (L)
1.7 (0.4)	0.34 (0.04)	6.65 (1.20)	17.2 (3.2)	5.6 (0.9)	8.2 (1.1)

The pharmacokinetics of fondaparinux are linear in the range of 2 to 8 mg by the subcutaneous route. At steady state, mean plasma concentration 2 hours post-dosing ranged between 0.32 and 0.47 mg/L in patients undergoing orthopaedic surgery receiving fondaparinux 2.5 mg.

In patients with symptomatic deep vein thrombosis and pulmonary embolism undergoing treatment with fondaparinux sodium injection 5 mg (< 50 kg), 7.5 mg (50–100 kg) and 10 mg (> 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

The distribution volume of fondaparinux is limited (7-11 litres) and is consistent with blood volume. Fondaparinux is highly (at least 97.0%) and specifically bound to ATIII protein and does not bind significantly to other plasma proteins, including platelet factor 4 (PF4).

Metabolism

There is no evidence that fondaparinux is metabolised.

Excretion

Fondaparinux is almost completely excreted by the kidney as unchanged compound. The elimination half-life ($t_{1/2}$) is about 17 hours in healthy young subjects and about 20 hours in healthy elderly subjects.

Special populations

Paediatric patients: Pharmacokinetic parameters of fondaparinux were characterized in a population pharmacokinetic analysis with sparse blood sampling data from 24 paediatric patients (1-18 years). Administration of a once daily 0.1 mg/kg subcutaneous dose to paediatric patients resulted in similar fondaparinux concentrations to that observed for adults administered recommended doses for the treatment of DVT or PE (see Section 5.1 Pharmacodynamic properties - Clinical trials). An adult bioequivalence study was employed to provide data for the population PK analysis. Fondaparinux has not

been investigated in this population for the prevention of VTE or for the treatment of superficial vein thrombosis or acute coronary syndrome (ACS).

Elderly patients: In patients over 75 years, the estimated plasma clearance was 1.2 to 1.4 times lower than in patients less than 65 years.

Renally impaired patients: Compared with patients with normal renal function (creatinine clearance > 80 mL/min) undergoing prophylaxis following orthopaedic surgery, plasma clearance is 1.2 to 1.4 times lower in patients with mild renal impairment (creatinine clearance 50 to 80 mL/min) and on average 2 times lower in patients with moderate renal impairment (creatinine clearance 30 to 50 mL/min). A similar pattern is observed in DVT and PE treatment patients.

IV Dosing - In severe renal impairment (creatinine clearance 10 - 30 mL/min), plasma clearance is approximately 5 times lower than in normal renal function. Associated terminal half-life values were 29 h in moderate and 72 h in patients with severe renal impairment.

Gender: No gender differences were observed after adjustment for body weight.

Race: Pharmacokinetic differences due to race have not been studied prospectively. However, studies performed in Asian (Japanese) healthy subjects did not reveal a different pharmacokinetic profile compared to caucasian healthy subjects. Similarly, no plasma clearance differences were observed between black and caucasian patients undergoing orthopaedic surgery.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Fondaparinux was not mutagenic in bacterial reverse mutation and mouse lymphoma cell forward mutation assays in vitro. It did not induce chromosomal aberrations in human lymphocytes in vitro or in bone marrow cells of rats in vivo.

Carcinogenicity

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

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The excipients are sodium chloride and water for injections.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

If fondaparinux sodium is added to a 0.9% saline mini-bag the product is chemically and physically stable for up to 6 h at 25°C. To reduce microbiological hazard, use as soon as practicable after preparation.

6.5 NATURE AND CONTENTS OF CONTAINER

ARIXTRA is available as pre-filled single use syringes consisting of a Type I glass barrel (1 mL) with a 27 gauge x 12.7 mm needle and an automatic safety system.

2.5 mg ARIXTRA in 0.5 mL single dose pre-filled syringe, with a blue plunger and an automatic safety system. Pack sizes of 2, 10 and 20 pre-filled syringes.

5.0 mg ARIXTRA in 0.4 mL single dose pre-filled syringe, with a orange plunger and an automatic safety system. Pack sizes of 7, 10 and 15 pre-filled syringes.

7.5 mg ARIXTRA in 0.6 mL single dose pre-filled syringe, with a magenta plunger and an automatic safety system. Pack sizes of 7, 10 and 15 pre-filled syringes.

10.0 mg ARIXTRA in 0.8 mL single dose pre-filled syringe, with a violet plunger and an automatic safety system. Pack sizes of 7, 10 and 15 pre-filled syringes.

Not all strengths or pack sizes are being distributed in Australia.

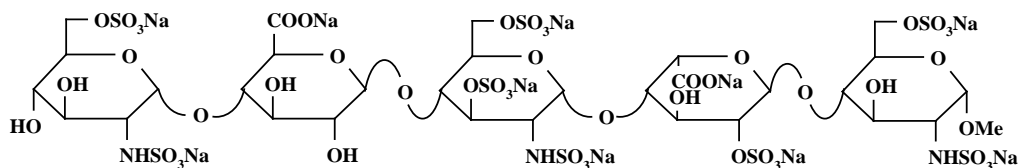
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Fondaparinux sodium is a white to almost white powder which is highly soluble in water and in dilute alkali solution, but insoluble in ethanol.

Chemical structure



MW = 1728 C₃₁H₄₃N₃Na₁₀O₄₉S₈

CAS number

114870-03-0

Attachment AusPAR Arixtra Fondaparinux Aspen Australia PM-2017-03032-1-3 Final 11 May 2020.
This is the Product Information that was approved with the submission described in this AusPAR. It may have been superseded. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4

8 SPONSOR

Aspen Pharmacare Australia Pty Ltd
34-36 Chandos Street
St Leonards NSW 2065
<http://www.aspenpharma.com.au>

9 DATE OF FIRST APPROVAL

15 April 2013

10 DATE OF REVISION

1 April 2020

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
	Reformatted as per TGA guidelines 2019