ARIXTRA™

Fondaparinux sodium (fondaparinux)

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each syringe contains 2.5 mg of fondaparinux sodium in 0.5 ml solution for injection.
The solution is a clear and colourless liquid.
Each syringe contains 5.0 mg of fondaparinux sodium in 0.4 ml solution for injection.
The solution is clear and colourless to slightly yellow.
Each syringe contains 7.5 mg of fondaparinux sodium in 0.6 ml solution for injection.
The solution is clear and colourless to slightly yellow.
Each syringe contains 10.0 mg of fondaparinux sodium in 0.8 ml solution for injection.
The solution is clear and colourless to slightly yellow.
PHARMACEUTICAL FORM
Injectable solution for subcutaneous and intravenous use.
CLINICAL PARTICULARS
Indications
Prevention of Venous Thromboembolic Events (VTE) in patients undergoing major orthopaedic surgery of the lower limbs such as:
- hip fracture, including extended prophylaxis;
- knee replacement surgery;
- hip replacement surgery.

Prevention of Venous Thromboembolic Events (VTE) in patients undergoing abdominal surgery who are at risk of thromboembolic complications.
Prevention of Venous Thromboembolic Events (VTE) in medical patients who are at risk of thromboembolic complications due to restricted mobility during acute illness.
Treatment of acute Deep Vein Thrombosis (DVT).
Treatment of acute Pulmonary Embolism (PE).
Treatment of unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI) acute coronary syndrome for the prevention of death, myocardial infarction and refractory ischaemia. *ARIXTRA* has been shown to reduce all cause mortality in patients with UA/NSTEMI.
Treatment of ST segment elevation myocardial infarction (STEMI) acute coronary syndrome for the prevention of death and myocardial re-infarction in patients who are managed with thrombolytics or who initially are to receive no other form of reperfusion therapy. *ARIXTRA* has been shown to reduce all cause mortality in patients with STEMI.
Dosage and Administration
Method of administration
- ***Subcutaneous administration***

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 the injection. The whole length of the needle should be inserted perpendicularly into a skin fold held between the thumb and the forefinger. The skin fold should be held throughout the injection.
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. Instruction for self-administration is included in the package leaflet *(see Instructions for Use/Handling)*.
- ***Intravenous administration (first dose in STEMI patients only)***

Intravenous administration should be through an existing intravenous line either directly or using a small volume (25 or 50ml) 0.9% saline minibag. 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.
- **Adults**

PREVENTION OF VTE
Orthopaedic and abdominal surgery: the recommended dose of *ARIXTRA* is 2.5 mg once daily, administered post-operatively by subcutaneous injection.
The timing of the first dose should be no earlier than 6 hours following surgical closure, and only after haemostasis has been established *(see Warnings and Precautions)*.
Treatment should be continued until the risk of venous thrombo-embolism has diminished, usually until the patient is ambulant, at least 5 to 9 days after surgery. Experience shows that in patients undergoing hip fracture surgery, the risk of VTE continues beyond 9 days after surgery. In these patients the use of prolonged prophylaxis with *ARIXTRA* should be considered for up to an additional 24 days *(see Clinical Studies)*.

Medical patients at risk of thromboembolic complications: the recommended dose of *ARIXTRA* is 2.5 mg once daily administered by subcutaneous injection. A treatment duration of 6 to 14 days has been clinically studied in medical patients *(see Clinical Studies)*.
TREATMENT OF DVT AND PE
The recommended dose of *ARIXTRA* to be administered by subcutaneous injection once daily is:
- 5 mg for body weight less than 50 kg;
- 7.5 mg for body weight 50 to 100 kg;
- 10 mg for body weight greater than 100 kg.

Treatment should be continued for at least 5 days and until adequate oral anticoagulation is established (International Normalised Ratio 2 to 3). Concomitant treatment with vitamin K antagonists should be initiated as soon as possible, usually within 72 hours. The usual duration of *ARIXTRA* treatment is 5 to 9 days *(see Clinical Studies)*.
TREATMENT 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 continued for up to 8 days or until hospital discharge.
If a patient is to undergo percutaneous coronary intervention (PCI) while on *ARIXTRA*, 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 *ARIXTRA (see Warnings and Precautions)*.
The timing of restarting subcutaneous *ARIXTRA* after sheath removal should be based on clinical judgment. In the UA/NSTEMI clinical trial 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.
TREATMENT 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.
If a patient is to undergo non-primary percutaneous coronary intervention (PCI) while on *ARIXTRA*, 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 *ARIXTRA (see Warnings and Precautions)*.
The timing of restarting subcutaneous *ARIXTRA* after sheath removal should be based on clinical judgment. In the STEMI clinical trial treatment with *ARIXTRA* was restarted no earlier than 3 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.
Special Populations
- **Children**

The safety and efficacy of *ARIXTRA* in patients under the age of 17 has not been established *(see Clinical Studies)*.
- **Elderly (from 75 years)**

ARIXTRA should be used with caution in elderly patients as renal function decreases with age *(see Renal impairment, Warnings and Precautions)*. In patients **undergoing surgery**, the timing of the first dose of *ARIXTRA* requires strict adherence *(see Warnings and Precautions)*.
- **Patients with body weight less than 50 kg**

Patients with body weight below 50 kg are at increased risk of bleeding *(see Warnings and Precautions)*. In patients **undergoing surgery**, the timing of the first dose of *ARIXTRA* requires strict adherence *(see Warnings and Precautions)*.
- **Renal impairment**

Prevention of VTE
No dosage reduction is required in patients with a creatinine clearance greater than or equal to 30 ml/min.
In patients with a creatinine clearance of between 20 to 30 ml/min in whom the physician determines that the benefit of thromboprophylaxis exceeds the risk, a dose of 2.5 mg on alternate days (each dose approximately 48 hours apart) is recommended *(see Warnings and Precautions, Pharmacokinetics)*.
ARIXTRA is not recommended for use in patients with a creatinine clearance of less than 20 ml/min *(see Warnings and Precautions)*.
In patients undergoing surgery, the timing of the first dose of *ARIXTRA* requires strict adherence.
Treatment of VTE
No dosage reduction is required in patients with a creatinine clearance greater than or equal to 30 ml/min.
ARIXTRA should not be used in patients with a creatinine clearance of less than 30 ml/min *(see Warnings and Precautions)*.
Treatment of UA/NSTEMI and STEMI
ARIXTRA is not recommended for use in patients with a creatinine clearance of less than 20 ml/min *(see Warnings and Precautions)*. No dosage reduction is required for patients with a creatinine clearance greater than or equal to 20 ml/min.
- **Hepatic impairment**

No dosing adjustment of *ARIXTRA* is necessary in patients with mild to moderate hepatic impairment *(see Pharmacokinetics)*. In patients with severe hepatic impairment, *ARIXTRA* should be used with caution *(see Warnings and Precautions)*.

Contraindications
- known hypersensitivity to *ARIXTRA* or any of the excipients.
- active clinically significant bleeding.
- acute bacterial endocarditis.

Warnings and Precautions
Route of administration - *ARIXTRA* must not be administered intramuscularly *(see Dosage and Administration)*.
PCI and risk of guiding catheter thrombus - In STEMI patients undergoing primary PCI for reperfusion, the use of *ARIXTRA* prior to and during PCI is not recommended. In UA/NSTEMI and STEMI patients undergoing non-primary PCI, the use of *ARIXTRA* as the sole anticoagulant during PCI is not recommended, therefore UFH should be used according to standard practice *(see Dosage and Administration)*.
In a clinical trial comparing two dose regimens of UFH during non-primary PCI, fondaparinux-treated UA/NSTEMI patients were randomized to receive either 'standard dose UFH' (median dose 85IU/kg) or 'low dose UFH' (median dose 50IU/kg). The incidence of peri-PCI major bleeding was 1.2% with 'standard dose UFH' and 1.4% with 'low dose UFH' *(see Clinical Studies)*.
Clinical trials have shown a low but increased risk of guiding catheter thrombus in patients treated solely with *ARIXTRA* for anticoagulation during PCI compared to control. Incidences in non-primary PCI in UA/NSTEMI were 1.0% vs 0.3% (*ARIXTRA* vs. enoxaparin) and in primary PCI in STEMI were 1.2% vs 0% (*ARIXTRA* vs. control). In fondaparinux-treated UA/NSTEMI patients randomised to receive "standard dose" or "low dose" regimens of UFH during non-primary PCI, the incidences of catheter thrombus were 0.1% and 0.5%, respectively *(see Clinical Studies)*.
Haemorrhage - *ARIXTRA*, like other anticoagulants must be used with caution in conditions with an increased risk of haemorrhage, (such as congenital or acquired bleeding disorders, active ulcerative gastrointestinal disease, recent intracranial haemorrhage, shortly after brain, spinal or ophthalmic surgery).
- ***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 *ARIXTRA*. If co-administration is essential, close monitoring is recommended *(see Interactions)*.
- ***Prevention of VTE following surgery (timing of first ARIXTRA 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.
- ***Treatment of UA/NSTEMI and STEMI***

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

***Spinal/epidural anaesthesia/spinal puncture* - Epidural or spinal haematomas that may result in long-term or permanent paralysis can occur with the use of anticoagulants and spinal/epidural anaesthesia or spinal puncture. The risk of these rare events may be higher with post-operative use of indwelling epidural catheters or the concomitant use of other medicinal products affecting haemostasis.**
Elderly patients - The elderly population is at increased risk of bleeding. As renal function generally decreases with age, elderly patients may show reduced elimination and increased exposure of *ARIXTRA*. *ARIXTRA* should be used with caution in elderly patients *(see Dosage and Administration)*.
Low body weight - Patients with body weight less than 50 kg are at increased risk of bleeding. Elimination of *ARIXTRA* decreases with weight decrease. *ARIXTRA* should be used with caution in these patients *(see Dosage and Administration)*.
Renal impairment - The plasma clearance of fondaparinux decreases with the severity of renal impairment, and is associated with an increased risk of haemorrhage *(see Pharmacokinetics)*.
Patients with renal impairment, particularly those with a creatinine clearance of less than 30 ml/min are at increased risk of both major bleeding episodes and VTE.
- ***Prevention of VTE***

There are limited clinical data available for the use of fondaparinux for prevention of VTE in patients with creatinine clearance less than 20 ml/min. Therefore, *ARIXTRA* is not recommended for prevention of VTE in these patients *(see Dosage and Administration, Pharmacokinetics)*.
- ***Treatment of VTE***

There are limited clinical data available for the use of fondaparinux for treatment of VTE in patients with creatinine clearance of less than 30 ml/min. Therefore, *ARIXTRA* is not recommended for the treatment of VTE in these patients *(see Dosage and Administration, Pharmacokinetics)*.
- ***Treatment of UA/NSTEMI and STEMI***

There are limited clinical data available on the use of *ARIXTRA* for the treatment of UA/NSTEMI and STEMI in patients with creatinine clearance between 20 to 30 ml/min. Therefore the physician should determine if the benefit of treatment outweighs the risk *(see Dosage and Administration and Pharmacokinetics)*. *ARIXTRA* is not recommended in patients with a creatinine clearance of less than 20 ml/min.
Severe hepatic impairment - In patients with an elevation in prothrombin time, the use of *ARIXTRA* should be considered with caution, because of an increased risk of bleeding due to a possible deficiency of coagulation factors in patients with severe hepatic impairment *(see Dosage and Administration)*.

Heparin Induced Thrombocytopenia - *ARIXTRA* does not bind to platelet factor 4 and does not cross-react with sera from patients with Heparin Induced Thrombocytopenia (HIT)-type II. It should be used with caution in patients with a history of HIT. The efficacy and safety of *ARIXTRA* have not been formally studied in HIT-type II. Rare spontaneous reports of HIT in patients treated with *ARIXTRA* have been received. To date a causal association between treatment with *ARIXTRA* and the occurrence of HIT has not been established.
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.
Interactions
Fondaparinux does not markedly inhibit CYP450s (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4) *in vitro*. Thus, *ARIXTRA* 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.
In clinical studies performed with fondaparinux, the concomitant use of warfarin (oral anticoagulant), acetylsalicylic acid (platelet inhibitor), piroxicam (non-steroidal anti-inflammatory), and digoxin (cardiac glycoside) did not significantly affect the pharmacokinetics or pharmacodynamics of fondaparinux. In addition fondaparinux neither influenced the INR activity of warfarin, nor the bleeding time under acetylsalicylic acid or piroxicam treatment, nor the pharmacokinetics or pharmacodynamics of digoxin at steady state.
Pregnancy and Lactation
Pregnancy
There are limited clinical data available on exposed pregnancies. *ARIXTRA* should not be prescribed to pregnant women unless the benefit outweighs the risk *(see Non-Clinical Information)*.
Lactation
Fondaparinux is excreted in rat milk but it is not known whether fondaparinux is excreted in human milk.
Breast-feeding is not recommended during treatment with *ARIXTRA*.
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.
Adverse Reactions
Adverse reactions are listed below by system organ class and frequency and indication. Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100, <1/10), uncommon (≥ 1/1,000, <1/100), rare (≥ 1/10,000, <1/1,000), very rare (< 1/10,000). These adverse reactions should be interpreted within the surgical or medical context of the indications.
Clinical Trial Data
Infections and infestations
Rare: Post-operative wound infections.
Blood and lymphatic system disorders
Common: Anaemia, bleeding (various sites including rare cases of intracranial/ intracerebral and retroperitoneal bleedings), purpura.
Uncommon: Thrombocytopenia, thrombocythaemia, abnormal platelets, coagulation disorder.
Immune system disorders
Rare: Allergic reaction.
Metabolism and nutrition disorders
Rare: Hypokalaemia.
Nervous system disorders
Uncommon: Headache.
Rare: Anxiety, confusion, dizziness, somnolence, vertigo.
Vascular disorders
Rare: Hypotension.
Respiratory, thoracic and mediastinal disorders
Rare: Dyspnoea, coughing.
Gastrointestinal disorders
Uncommon: Nausea, vomiting.
Rare: Abdominal pain, dyspepsia, gastritis, constipation, diarrhoea.
Hepatobiliary disorders
Uncommon: Abnormal liver function tests, hepatic enzymes increased.
Rare: Bilirubinaemia.
Skin and subcutaneous tissue disorders
Uncommon: Rash, pruritus, wound secretion.
General disorders and administration site conditions
Common: Oedema.
Uncommon: Fever.
Rare: Reaction at injection site, chest pain, leg pain, fatigue, flushing, syncope.

Overdose
Symptoms and Signs
ARIXTRA doses above the recommended regimen may lead to an increased risk of bleeding.
Treatment
Overdose 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.
PHARMACOLOGICAL PROPERTIES
Pharmacodynamics
Pharmacotherapeutic group: antithrombotic agents.
ATC Code
B01AX05
Mechanism of Action
Fondaparinux is a synthetic and selective inhibitor of activated Factor X (Xa). The antithrombotic 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 neutralization of Factor Xa by ATIII. 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 known effect on platelet function.
Pharmacodynamic Effects
At the 2.5 mg dose, fondaparinux does not have a clinically relevant affect on routine coagulation tests, such as activated partial thromboplastin time (aPTT), activated clotting time (ACT) or prothrombin time (PT)/International Normalised Ratio (INR) tests in plasma, nor bleeding time or fibrinolytic activity. However, rare spontaneous reports of elevated aPTT have been received at the 2.5mg dose.
Fondaparinux does not cross-react with sera from patients with Heparin Induced Thrombocytopenia (HIT) type II.
Anti-Xa activity
The pharmacodynamics/pharmacokinetics of fondaparinux 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 concentration of fondaparinux is expressed as milligrams of the fondaparinux calibrator/litre.
Pharmacokinetics
Absorption
After subcutaneous dosing, fondaparinux is completely and rapidly absorbed (absolute bioavailability 100%). Following a single subcutaneous injection of *ARIXTRA* 2.5 mg to young healthy subjects, peak plasma concentration, mean C_{max} of 0.34 mg/L, is reached in approximately 2 hours. Plasma concentrations of half the mean C_{max} values are reached 25 min post-dosing.
In elderly healthy subjects, pharmacokinetics of fondaparinux are linear in the range of 2 to 8 mg by subcutaneous route. Following once daily subcutaneous dosing, steady state of plasma levels is obtained after 3 to 4 days with a 1.3-fold increase in C_{max} and AUC. Following a single i.v. bolus administration to healthy elderly subjects, the pharmacokinetics of fondaparinux are linear over the therapeutic range.
In patients undergoing hip replacement surgery receiving *ARIXTRA* 2.5 mg once daily subcutaneously, the peak steady-state plasma concentration is, on average, 0.39 to 0.50 mg/L and is reached approximately 3 hours post-dose. In these patients, the minimum steady-state plasma concentration is 0.14 to 0.19 mg/L.
In patients with symptomatic deep vein thrombosis and pulmonary embolism undergoing treatment with *ARIXTRA* 5 mg (body weight less than 50 kg), 7.5 mg (body weight 50 to 100 kg) and 10 mg (body weight greater than 100 kg) subcutaneously once daily, the body-weight-adjusted doses provide similar mean steady-state peaks and minimum plasma concentrations across all body weight categories. The mean peak steady-state plasma concentration is in the range of 1.20 to 1.26 mg/L. In these patients, the mean minimum steady-state plasma concentration is in the range of 0.46 to 0.62 mg/L.
Distribution
In healthy adults, intravenously or subcutaneously administered fondaparinux distributes mainly in blood and only to a minor extent in extravascular fluid, as demonstrated by steady state and non-steady state apparent volume of distribution of 7 to 11 L. *In vitro*, fondaparinux is highly (at least 94%) and specifically bound to antithrombin III (ATIII) and does not bind significantly to other plasma proteins, including platelet Factor 4 (PF4) or red blood cells.
Metabolism
In vivo metabolism of fondaparinux has not been investigated since the majority of the administered dose is eliminated unchanged in urine in individuals with normal kidney function.
Elimination
Fondaparinux is eliminated in urine mainly as unchanged drug. In healthy individuals, 64 to 77% of a single subcutaneous or intravenous dose is eliminated in urine in 72 hours. The elimination half-life is about 17 hours in healthy young subjects and about 21 hours in healthy elderly subjects. In patients with normal renal function, the mean fondaparinux clearance is 7.82 mL/min.

Special Patient Populations
- **Renal impairment**

Fondaparinux elimination is prolonged in patients with renal impairment 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 impairment (creatinine clearance 50 to 80 ml/min), approximately 40% lower in patients with moderate renal impairment (creatinine clearance 30 to 50 ml/min) and approximately 55% lower in patients with severe renal impairment (less than 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 impairment. A similar relationship between fondaparinux clearance and extent of renal impairment was observed in DVT treatment patients.
Prevention of VTE
A population pharmacokinetic model was developed using data obtained from patients undergoing major orthopaedic surgery of the lower limbs (MOSLL) receiving fondaparinux and included patients with creatinine clearance as low as 23.5 ml/min. Pharmacokinetic simulations using this model showed that predicted average exposures of fondaparinux in patients with creatinine clearance between 20-30 ml/min receiving 2.5 mg on alternate days were similar to those seen in patients with mild to moderate renal impairment (creatinine clearance 30 to 80 ml/min) receiving 2.5 mg once daily *(see Dosage and Administration, Warnings and Precautions)*.
- **Hepatic impairment**

Unbound concentrations of fondaparinux are expected to be unchanged in patients with mild to moderate hepatic impairment, and therefore, no dose adjustment is necessary based on pharmacokinetics. Following a single, subcutaneous dose of fondaparinux in subjects with moderate hepatic impairment (Child-Pugh Category B), Cmax 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 impairment thereby resulting in increased renal clearance of fondaparinux.
The pharmacokinetics of *ARIXTRA* has not been studied in patients with severe hepatic impairment *(see Dosage and Administration, Warnings and Precautions)*.
- **Children**

Pharmacokinetic parameters of *ARIXTRA* 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 exposure to that observed for adults administered recommended doses for the treatment of DVT or PE *(see Clinical Studies)*.
- **Elderly**

Fondaparinux elimination is prolonged in patients over 75 years old. In studies evaluating *ARIXTRA* 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 relationship between fondaparinux clearance and age was observed in DVT treatment patients.
- **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, based on the results of population pharmacokinetic analysis conducted in patients undergoing orthopaedic surgery, no plasma clearance differences were observed between black and Caucasian patients.
- **Body weight**

In patients weighing less than 50 kg the total clearance of fondaparinux sodium is decreased by approximately 30% *(see Warnings and Precautions)*.
Clinical Studies
Prevention of venous thromboembolic events (VTE) in patients undergoing major orthopaedic surgery of the lower limbs treated up to 9 days
The clinical program included patients undergoing major orthopaedic surgery of the lower limbs such as hip fracture, major knee surgery or hip replacement surgery. *ARIXTRA* 2.5 mg once daily started 6 to 8 hours postoperatively was compared with enoxaparin 40 mg once daily started 12 hours before surgery, or 30 mg twice daily started 12 to 24 hours after surgery. Both treatments were administered for 7 ± 2 days.
In a pooled analysis of these studies, *ARIXTRA* was associated with a significant decrease in VTE compared to enoxaparin (6.8% versus 13.7%, respectively), irrespective of the type of surgery performed. The majority of endpoint events consisted mainly of distal DVT, but the incidence of proximal DVT was also significantly reduced. The incidence of symptomatic VTE, including PE was not significantly different between treatment groups.
In studies versus enoxaparin 40 mg once daily started 12 hours before surgery, major bleeding was observed in 3.3% of *ARIXTRA* patients treated with the recommended dose, compared to 2.6% with enoxaparin. In patients treated with *ARIXTRA* according to the recommended regimen (6 hours after surgery), the rate of major bleeding was 2.8 %. In studies versus enoxaparin 30 mg twice daily started 12 to 24 hours after surgery, major bleeding was observed in 1.9% of *ARIXTRA* patients treated with the recommended dose, compared to 1.1% with enoxaparin.

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Extended prophylaxis: Prevention of venous thromboembolic events (VTE) in patients undergoing hip fracture surgery treated for up to 24 days following an initial prophylaxis of 1 week

Following treatment with 2.5 mg *ARIXTRA* for 7 ± 1 day, hip fracture surgery patients were randomised to receive *ARIXTRA* 2.5 mg once daily or placebo for an additional 21 ± 2 days.

Extended prophylaxis with *ARIXTRA* provided a significant reduction in the overall rate of VTE compared with placebo (1.4% versus 35%, respectively). *ARIXTRA* also provided a significant reduction in the rate of symptomatic VTE (0.3% versus 2.7%, respectively). Major bleeding, all at surgical site and none fatal, was observed in 2.4% *ARIXTRA* patients compared to 0.6% with placebo.

Prevention of VTE in patients undergoing abdominal surgery at risk of thromboembolic events

Patients were randomised to receive either *ARIXTRA* 2.5 mg once daily or dalteparin 5000 IU once daily, with one 2500 IU preoperative injection and a first 2500 IU post-operative injection, for 7 ± 2 days following abdominal surgery. *ARIXTRA* was non-inferior to dalteparin (VTE rates 4.6% versus 6.1%, respectively). The incidence of symptomatic VTE was similar between treatment groups (0.4 % on *ARIXTRA* versus 0.3% on dalteparin).

In patients undergoing cancer surgery, representing the major subgroup of the clinical study (69% of the population) the VTE rate was 4.7 % in the *ARIXTRA* group versus 7.7% in the dalteparin group.

Major bleeding was observed in 3.4% of the patients in the *ARIXTRA* group and in 2.4% of the dalteparin group. In patients treated with *ARIXTRA* according to the recommended regimen (6 hours after surgery), the rate of major bleeding was 2.8 %.

Prevention of VTE in medical patients

Acutely ill medical patients, aged 60 years or older and expected to require bed rest for at least four days were randomised to receive either *ARIXTRA* 2.5 mg once daily or placebo for 6 to 14 days. *ARIXTRA* significantly reduced the overall rate of VTE compared to placebo (5.6% versus 10.5%, respectively). The majority of events were asymptomatic distal DVT. *ARIXTRA* also significantly reduced the rate of adjudicated fatal PE (0.0% versus 1.2%, respectively). Major bleeding was observed in one patient (0.2%) in each group.

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE)

- **DVT**

In patients with a confirmed diagnosis of acute symptomatic DVT, *ARIXTRA* 5 mg (body weight less than 50 kg), 7.5 mg (body weight 50 kg to 100 kg) or 10 mg (body weight greater than 100 kg) once daily, was compared to enoxaparin 1 mg/kg subcutaneously twice daily. Patients were treated for at least 5 days in conjunction with a vitamin K antagonist which was continued for 90 ± 7 days, with regular dose adjustments to achieve an INR of 2 to 3. *ARIXTRA* was demonstrated to be non-inferior to enoxaparin (VTE rates 3.9% and 4.1% at Day 97, respectively). Major bleeding during the initial treatment period was observed in 1.1% of *ARIXTRA* patients, compared to 1.2% with enoxaparin.

- **PE**

In patients with a confirmed diagnosis of acute symptomatic PE, *ARIXTRA* 5 mg (body weight less than 50 kg), 7.5 mg (body weight 50 kg to 100 kg) or 10 mg (body weight greater than 100 kg) once daily, was compared to unfractionated heparin (UFH) i.v. bolus (5000 IU), followed by a continuous iv infusion adjusted to maintain 1.5 to 2.5 times aPTT control value. Patients were treated for at least 5 days in conjunction with a Vitamin K antagonist which was continued for 90 ± 7 days, with regular dose adjustments to achieve an INR of 2 to 3.

ARIXTRA was demonstrated to be non-inferior to UFH (VTE rates 3.8% and 5.0% at Day 97, respectively). Major bleeding during the initial treatment period was observed in 1.3% of *ARIXTRA* patients, compared to 1.1% with UFH.

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

A double-blind, randomised, non-inferiority study (OASIS 5) assessed the safety and efficacy of *ARIXTRA* 2.5 mg subcutaneously once daily versus enoxaparin 1 mg/kg subcutaneously twice daily in approximately 20,000 patients with UA/NSTEMI. The median treatment duration was 6 days in the *ARIXTRA* treatment group and 5 days in the enoxaparin treatment group. The mean age of the patients was 67 years, and approximately 60% were aged at least 65 years. Approximately 40% and 17% of patients had mild (creatinine clearance 50 to less than 80 ml/min) or moderate (creatinine clearance 30 to less than 50 ml/min) renal impairment, respectively.

The primary adjudicated endpoint was a composite of death, myocardial infarction (MI) and refractory ischaemia (RI) within 9 days of randomisation. *ARIXTRA* was as effective as enoxaparin on the primary endpoint. Of the patients treated with *ARIXTRA* or enoxaparin, 5.8% and 5.7% of patients, respectively experienced an event by Day 9 (hazard ratio 1.01, 95% CI, 0.90, 1.13, one-sided non-inferiority p value = 0.003).

There was a 17% reduction in the risk of all-cause mortality in favour of *ARIXTRA* by Day 30 (*ARIXTRA*, 2.9%, enoxaparin, 3.5%, hazard ratio 0.83, 95% CI, 0.71, 0.97, p = 0.02) that was apparent by Day 14 (*ARIXTRA*, 2.1%, enoxaparin, 2.4%, hazard ratio 0.86, 95% CI, 0.72, 1.04, p = 0.14) and sustained to Day 180 (*ARIXTRA*, 5.7%, enoxaparin, 6.4%, hazard ratio 0.89, 95% CI, 0.80, 1.00, p = 0.05). The effects of *ARIXTRA* and enoxaparin on the incidence of MI and RI were similar at all time points. The efficacy findings were consistent across demographic subgroups, including elderly and renally impaired patients, and across the range of concomitant medications and interventions.

Treatment with *ARIXTRA* was associated with a statistically and clinically significant reduction in the incidence of major bleeding compared to enoxaparin. At Day 9 the incidence of major bleeding on *ARIXTRA* and enoxaparin was 2.1% and 4.1%, respectively (hazard ratio 0.52, 95% CI, 0.44, 0.61, p < 0.001). The lower incidence of major bleeding on *ARIXTRA* compared to enoxaparin was also observed consistently across demographic subgroups, including elderly and renally impaired patients, and when *ARIXTRA* was used concomitantly with aspirin, thienopyridines or GPIIb/IIa inhibitors.

In patients undergoing CABG surgery, the incidence of major bleeding at Day 9 was similar on *ARIXTRA* and enoxaparin (9.7% and 9.8% 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 3235 high-risk UA/NSTEMI patients scheduled for angiography and treated with open-label fondaparinux (OASIS 8/FUTURA), the 2026 patients indicated for PCI were randomised to receive one of two double-blind dose regimens of adjunctive 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.

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.

Outcomes	Incidence		Odds Ratio[1] (95%CI)	p-value
	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)	0.267
Secondary				
Peri-PCI major bleeding	1.4%	1.2%	1.14 (0.53, 2.49)	0.734
Peri-PCI minor bleeding	0.7%	1.7%	0.40 (0.16, 0.97)	0.042
Major vascular access site complications	3.2%	4.3%	0.74 (0.47, 1.18)	0.207
Peri-PCI major bleeding or death, MI or TVR at Day 30	5.8%	3.9%	1.51 (1.0, 2.28)	0.051
Death, MI or TVR at Day 30	4.5%	2.9%	1.58 (0.98, 2.53)	0.059

1: Odds ratio: Low Dose/Standard Dose

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

The incidences of 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-randomized patients experienced thrombus in the diagnostic catheter during coronary angiography. Twelve (0.37%) enrolled patients experienced thrombus in the arterial sheath, of these 7 were reported during angiography and 5 were reported during PCI.

Treatment of ST segment elevation myocardial infarction (STEMI)

A double blind, randomised study (OASIS 6) assessed the safety and efficacy of *ARIXTRA* 2.5 mg once daily up to 8 days, or until hospital discharge, versus usual care (placebo or UFH) in approximately 12000 patients with STEMI. All patients received standard treatments for STEMI at the investigators discretion, including reperfusion with primary PCI (31%), thrombolytics (45%) or no reperfusion (24%). The mean age of the patients was 61 years, and approximately 40% were aged at least 65 years. Approximately 40% and 14% of patients had mild (creatinine clearance 50 to less than 80 ml/min) or moderate (creatinine clearance 30 to less than 50 ml/min) renal impairment, respectively.

The primary adjudicated endpoint was a composite of death and recurrent myocardial infarction (re-MI) within 30 days of randomisation. *ARIXTRA* was superior to control on the primary endpoint. Of the patients treated with *ARIXTRA* or control, 9.7% and 11.1% respectively experienced an event by Day 30 (hazard ratio 0.86, 95% CI, 0.77, 0.96, p = 0.008). This statistically significant benefit was observed as early as Day 9 and was maintained through Day 180. There was a 13% reduction in the risk of all-cause mortality in favour of *ARIXTRA* at Day 30 (*ARIXTRA*, 7.9%, control, 8.9%, hazard ratio 0.87, 95% CI, 0.77, 0.98, p = 0.02) that was apparent by Day 9 (*ARIXTRA*, 6.1%, control, 7.0%, hazard ratio 0.86, 95% CI, 0.75, 0.99, p = 0.04) and sustained to Day 180 (*ARIXTRA*, 9.9%, control, 11.1%, hazard ratio 0.88, 95% CI, 0.79, 0.99, p = 0.03).

In patients for whom a thrombolytic was chosen as the reperfusion strategy, *ARIXTRA* reduced the risk of death and re-MI at Day 30. Of the patients receiving thrombolytics treated with *ARIXTRA* or control, 10.9% and 13.6%, respectively experienced an event by Day 30 (hazard ratio 0.79, 95% CI, 0.68, 0.93, p = 0.003).

In patients for whom primary PCI was chosen as the reperfusion strategy, there was no efficacy benefit with *ARIXTRA*. The incidence of death and re-MI at Day 30 in patients treated with *ARIXTRA* and control were 6.0% and 4.8%, respectively (hazard ratio 1.26, 95% CI, 0.96, 1.66, p = 0.1).

In patients who were treated without primary PCI or thrombolytic, *ARIXTRA* reduced the risk of death and re-MI at Day 30. Of the patients treated with *ARIXTRA* or control, 12.1% and 15.0% respectively experienced an event by Day 30 (hazard ratio 0.79, 95% CI, 0.65, 0.97, p = 0.023). The efficacy findings were consistent across demographic subgroups, including elderly and renally impaired patients, and across the range of concomitant medications.

Treatment with *ARIXTRA* was not associated with an increased risk of bleeding in the overall population or in demographic subgroups, including the elderly and renally impaired, and when used concomitantly with aspirin and thienopyridines. Overall, 1.1% of patients treated with *ARIXTRA* and 1.4% of control patients experienced a severe haemorrhage, defined according to modified thrombolysis in myocardial infarction criteria (TIMI), by Day 9.

In patients for whom a thrombolytic was chosen as the reperfusion strategy, the incidence of severe haemorrhage at Day 9 was 1.3% on *ARIXTRA* and 2.0% on control. In patients for whom primary PCI was chosen as the reperfusion strategy, the incidence of severe haemorrhage at Day 9 was 1.0% on *ARIXTRA* and 0.4% on control. In patients who were treated without primary PCI or thrombolytic, the incidence of severe haemorrhage at Day 9 was 1.2% on *ARIXTRA* and 1.5% on control.

In patients (n=234) undergoing non-primary PCI, where it was recorded that they received adjunct UFH for anticoagulation during the procedure (238 procedures), the incidence of severe haemorrhage occurring post-PCI was low and similar for *ARIXTRA* (2.1%; 5 cases) and control (1.3%;3 cases) at Day 9.

In *ARIXTRA*-treated STEMI patients undergoing non-primary PCI [n=311 (318 procedures)], in whom UFH was recommended for anticoagulation during the procedure, one event of guiding catheter thrombus was reported. However, this patient received UFH as treatment for the event of catheter thrombus rather than pre-PCI.

Approximately 1% of patients underwent CABG surgery. In these patients the incidence of severe haemorrhage at Day 9 was 6.9% on *ARIXTRA* and 17.1% on control.

Use in Paediatric Patients

Safety and effectiveness of *ARIXTRA* 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 *ARIXTRA*. 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). *ARIXTRA* was administered at an initial dose of 0.1 mg/kg subcutaneously once daily. Dosing was adjusted to achieve peak fondaparinux sodium concentrations (0.5 to 1 mg/L). One patient received concomitant warfarin and *ARIXTRA* 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 *ARIXTRA* in a paediatric population. The majority of patients (88%) achieved target fondaparinux concentrations after the first dose of fondaparinux.

Pharmacokinetic modelling and simulation demonstrated that the 0.1 mg/kg once daily dose resulted in fondaparinux concentrations that were similar to those observed in adults receiving *ARIXTRA* for the treatment of DVT or PE. There were no apparent differences in achieving the target fondaparinux concentration range among age groups.

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 *ARIXTRA*. Minor gastrointestinal bleeding was reported in another patient on day 5 of therapy which resulted in temporary discontinuation of *ARIXTRA*.

Pre-clinical Safety Data

No long-term studies in animals have been performed to evaluate the carcinogenic potential of fondaparinux sodium. Fondaparinux sodium was not genotoxic in the Ames test, the mouse lymphoma cell (L5178Y/TK+/-) forward mutation test, the human lymphocyte chromosome aberration test, the rat hepatocyte unscheduled DNA synthesis (UDS) test, or the rat micronucleus test.

Reproduction studies have been performed in rats and rabbits at subcutaneous doses up to 10 mg/kg/day (approximately 5 and 12 times human exposure at a dose of 2.5 mg, or 2 and 4 times human exposure at a dose of 7.5 mg, based on AUC) and have revealed no evidence of impaired fertility or harm to the foetus due to fondaparinux sodium. Because animal reproduction studies are not always predictive of human response, *ARIXTRA* should not be prescribed to pregnant women unless the risk of VTE outweighs the potential risk to the foetus.

PHARMACEUTICAL PARTICULARS

List of Excipients

Sodium chloride
Water for injection
Hydrochloric acid or sodium hydroxide for pH adjustment as necessary.

Incompatibilities

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

Shelf-Life

The expiry date is indicated on the packaging.
If *ARIXTRA* is added to a 0.9% saline minibag it should ideally be infused immediately, but can be stored at room temperature for up to 24 hours.

Special Precautions for Storage

Do not freeze.

Nature and Contents of Container

ARIXTRA pre-filled single-use syringes are made of Type I glass barrel (1 ml) affixed with a 27 gauge x 12.7 mm needle and stoppered with a bromobutyl or chlorobutyl elastomer plunger stopper.

ARIXTRA 2.5 mg/0.5 ml is available in pack sizes of 2, 7, 10 and 20 pre-filled syringes with a blue plunger and an automatic safety system.

ARIXTRA 5.0 mg/0.4 ml is available in pack sizes of 2 and 10 pre-filled syringes with an orange plunger and an automatic safety system.

ARIXTRA 7.5 mg/0.6 ml is available in pack sizes of 2 and 10 pre-filled syringes with a magenta plunger and an automatic safety system.

ARIXTRA 10.0 mg/0.8 ml is available in pack sizes of 2 and 10 pre-filled syringes with a violet plunger and an automatic safety system.

Not all pack sizes may be marketed.

Instructions for Use/Handling

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

ARIXTRA is administered by subcutaneous or intravenous injection. It must not be administered by intramuscular injection.

The subcutaneous injection is administered in the same way as with a standard syringe. Intravenous administration should be through an existing intravenous line either directly or using a small volume (25 or 50ml) 0.9% saline minibag.

The *ARIXTRA* pre-filled syringe has been designed with an automatic needle protection system to prevent needle stick injuries following injection.

Instruction for self-administration by subcutaneous injection is included in the package leaflet.

Any unused product or waste material should be disposed of in accordance with local requirements.

Not all presentations are available in every country.

Step-by-step instructions

Parts of the syringes:

1. Needle shield
2. Plunger
3. Finger-grip
4. Security sleeve

Instructions for use

1. **Wash your hands thoroughly** with soap and water and dry them with a towel.
2. **Remove the syringe from the carton and check that:**
   - the expiry date has not passed
   - the 2.5 mg solution is clear and colourless and doesn't contain particles
   - the 5, 7.5 and 10 mg solution is clear and colourless to slightly yellow and doesn't contain particles
   - the syringe has not been opened or damaged.
3. **Sit or lie down in a comfortable position.**
   Choose a place in the lower abdominal (tummy) area, at least 5 cm below your belly button (picture **A**).

   Alternate the left and right side of the lower abdominal area at each injection. This will help to reduce the discomfort at the injection site.

   If injecting in the lower abdominal area is not possible, ask your nurse or doctor for advice.

Picture A

4. **Clean the injection area with an alcohol wipe.**
5. **Remove the needle shield,** by first twisting it (picture **B1**) and then pulling it in a straight line away from the body of the syringe (picture **B2**).

   Discard the needle shield.

   Important note:
   - **Don't touch the needle** or allow it to touch any surface before the injection

   It is normal to see a small air bubble in this syringe. **Don't try to remove this air bubble before making the injection** - you may lose some of the medicine if you do.

Picture B1

Picture B2

6. **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 (picture **C**).

Picture C

7. **Hold the syringe firmly by the finger grip.** Insert the full length of the needle at right angles into the skin fold (picture **D**).

Picture D

8. **Inject ALL of the contents of the syringe by pressing down on the plunger as far as it goes.**
   (picture **E**).

Picture E

9. **Release the plunger** and the needle will automatically withdraw from the skin and go back into the security sleeve where it will be locked permanently (picture **F**).

Picture F

Do not dispose of the used syringe in the household waste. Dispose of it as your doctor or pharmacist has instructed.

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