- Arixtra Logo-

Fondaparinux sodium

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.

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;
- 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 unstable angina or non-ST segment elevation myocardial infarction (UA/ NSTEMI) in patients for whom an urgent (< 120 mins) invasive management (PCI) is not indicated (*see sections Warnings and Precautions & Pharmacological Properties*).

Treatment of ST segment elevation myocardial infarction (STEMI) in patients who are managed with thrombolytics or who initially are to receive no other form of reperfusion therapy (*see sections Warnings and Precautions & Pharmacological Properties*).

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 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**

ARIXTRA should not be used in patients with a creatinine clearance less than 30 ml/min (*See Warnings and Precautions*). No dosage reduction is required in patients with a creatinine clearance greater than or equal to 30 ml/min. In patients undergoing surgery, the timing of the first dose of ARIXTRA requires strict adherence.

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.
- severe renal impairment in
  - venous thromboembolic events (creatinine clearance less than 30 ml/min).
  - acute coronary events (creatinine clearance less than 20 ml/min).

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 85U/kg) or ‘low dose UFH’ (median dose 50U/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*). Due to the limited clinical data available, ARIXTRA should not be used in patients with severe renal impairment (creatinine clearance less than 30 ml/min).

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 the 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 (including very rare reports of angioedema, anaphylactoid/anaphylactic 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 effect 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. Due to the limited clinical data available, ARIXTRA should not be used in patients with severe renal impairment (*see Warnings and Precautions*).

- **Hepatic impairment**

Unbound concentration 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), C_{max} and AUC were decreased by 22% and 39%, respectively, as compared to subjects with normal liver function. The lower plasma concentrations of fondaparinux were attributed to reduced binding to ATIII secondary to the lower ATIII plasma concentrations in subjects with hepatic 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**

The use of ARIXTRA has not been investigated in children under the age of 17 years.

- **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 patient 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 2.5mg 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.

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 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/IIIa 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% CL)**	**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, 7.8%, 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 (1.7%; 4 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.

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

Store below 30°C. 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 pre-filled single-use syringes are available in pack sizes of 2’s and 10’s.

INSTRUCTIONS FOR USE/HANDLING

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

ARIXTRA is administered by subcutaneous injection 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.

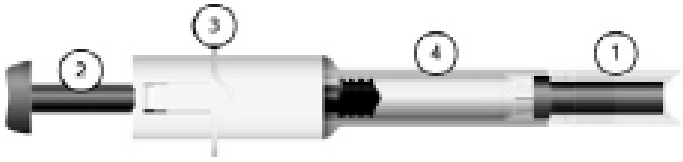
Any unused product or waste material should be disposed of in accordance with local requirements.

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

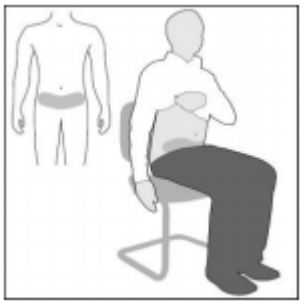
1. **Wash your hands thoroughly** with soap and water and dry them with a towel.

2. **Remove the syringe from the carton and check that:**
   - the expiry date has not passed
   - the solution is clear and colourless 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.

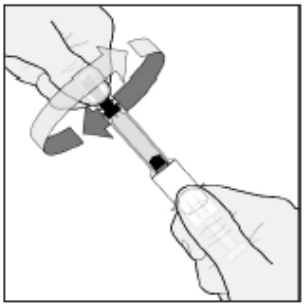
5. Remove the needle shield, by first twisting it (picture **B1**) and then pulling it in a straight line away from the body of the syringe (picture **B2**).

Discard the needle shield.

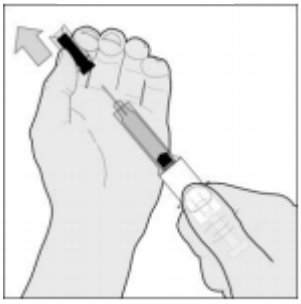
Important note:

- 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.

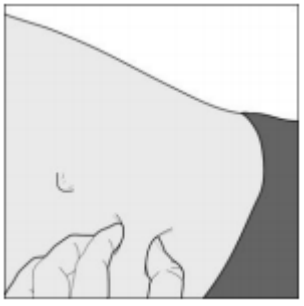


Picture B1



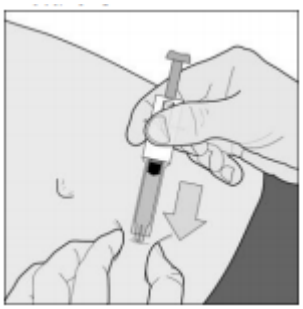
Picture B2

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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Date of revision: 15 Feb 2019