ARIXTRA™

Fondaparinux sodium

1. 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.

2. Pharmaceutical Form

Injectable solution for subcutaneous and intravenous use

3. Clinical Particulars

3.1 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) in patients for whom urgent (<120 mins) invasive management [Percutaneous Coronary Intervention (PCI)] is not indicated.

Adjunctive treatment of ST segmen elevation myocardial infarction (STEMI) in patients who are managed with thrombolytics or who initially are to receive no other form of reperfusion therapy.

3.2 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 50 ml) 0.9% saline minibag. To avoid the loss of medicinal product when using the pre-filled syringe do not expel the air bubble form 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 that occurs earlier.

If a patient is to undergo non-primary percutaneous coronary intervention (PCI) while on ARIXTRA™, unfractionated heparin (UFH) as per local 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 pivotal 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.

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 and treatment of VTE
AREXTRA™ should not be used in patients with a creatinine clearance of less than 30 ml/min *(See Warnings and Precautions and Pharmacokinetics).* No dosage reduction is required for 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 (*see Pharmacokinetics*). In patients with severe hepatic impairment, ARIXTRA™ should be used with caution *(see Warnings and Precautions*).

3.3 Contraindications
- Known hypersensitivity to ARIXTRA™ or any of the excipients.
- Active clinically significant bleeding.
- Acute bacterial endocarditis.
- Severe renal impairment defined by creatinine < 20 ml/min

3.4 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. Similarly, in UA/NSTEMI patients with life threatening conditions that require urgent revascularisation, the use of ARIXTRA™ prior to and during PCI is not recommended. These are patients with refractory or recurrent angina associated with dynamic ST deviation, heart failure, lifethreatening arrhythmias or haemodynamic instability. 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 local practice *(see Dosage and Administration*).

There are limited data on the use of UFH during non-primary PCI in patients treated with ARIXTRA™ (see clinical studies).

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

Clinical trial have shown a low but increased risk of guiding catheter thrombus in patients treated 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).

Haemorrhage - ARIXTRA™, like other anticoagulants should 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).

Agents that may enhance the risk of haemorrhage should not be administered concomitantly with fondaparinux. These agents include desirudin, fibrinolytic agents, GP IIb/IIIa receptor antagonists, heparin, heparinoids, or Low Molecular Weight Heparin (LMWH). Other antiplatelet medicinal products (acetylsalicylic acid, dipyridamole, sulfinpyrazone, ticlopidine or clopidogrel), and NSAIDs should be used with caution. If co-administration is essential, close monitoring is necessary.

- ***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. Patients 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 for prevention and treatment of VTE, ARIXTRA™ should not be used in patients with a creatinine clearance less than 30 ml/min.

For the treatment of UA/NSTEMI and STEMI, there are limited clinical data available on the use of ARIXTRA™ 2.5 mg once daily 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. No clinical experience exists form the use of ARIXTRA™ in patients with Heparin Induced Thrombocytopenia (HIT)-type II, and ARIXTRA™ should not be used in such patients.

3.5 Interactions

Fondaparinux does not markedly inhibit CYP450s (CYPlA2, 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.

Bleeding risk is increased with concomitant administration of fondaparinux and agents that may enhance the risk of haemorrhage (se warnings and precautions).

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 acetyl salicylic acid or piroxicam treatment, nor the pharmacokinetics or pharmacodynamics of digoxin at steady state.

Follow-up therapy with another anticoagulant medicinal product
If follow-up treatment is to be initiated with heparin or LMWH, the first injection should, as a general rule, be given one day after the last fondaparinux injection.

If follow-up treatment with a Vitamin K antagonists is required, treatment with fondaparinux should be continued until the target INR value has been reached.

3.6 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™.

3.7 Effects on Ability to Drive and Use Machines

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

3.8 Adverse Reactions

The safety of fondaparinux 2.5 mg has been evaluated in

- 3,595 patients undergoing major orthopaedic surgery of the lower limbs treated up to 9 days
- 327 patients undergoing hip fracture surgery treated for 3 weeks following an initial prophylaxis of 1 week
- 1407 patients undergoing abdominal surgery treated up to 9 days
- 425 medical patients who are at risk for thromboembolic complications treated up to 14 days
- 10,057 patients undergoing treatment of UA or NSTEMI ACS.
- 6,036 patients undergoing treatment of STEMI ACS.

Adverse reactions are listed below by system organ class and frequency and indication. Frequencies are defined as: very common (≥1/10), common (≥/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

Undesirable effects in patients undergoing major orthopaedic surgery of lower limbs and/or abdominal surgery :

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 I

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, wound secretion, oedema peripheral
Rare:	Reaction at injection site, chest pain, leg pain, fatigue, oedema genital, flushing, syncope.

Undesirable effects in medical patients :

Blood and lymphatic system disorders

Common:	Bleeding (haematoma, haematuria, haemoptysis, gingival bleeding)
Uncommon:	Anaemia

Respiratory, thoracic and mediastinal disorders

Uncommon:	Dyspnoea

Skin and subcutaneous tissue disorders

Uncommon:	Rash, pruritus

General disorders and administration site conditions

Uncommon:	Chest pain

In order studies or in post-marketing experience, rare cases of intracranial/intracerebral and retroperitoneal bleedings have been reported.

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

Bleeding was a commonly reported event in patients with UA/NSTEMI and STEMI. The incidence of adjudicated major bleeding was 2.1 % (fondaparinux) vs. 4.1% (enoxaparin) up to and including Day 9 in the Phase III UA/NSTEMI study, and the incidence of adjudicated severe haemorrhage by modified TIMI criteria was 1.1% (fondaparinux) vs. 1.4% (control [UFH/placebo]) up to and including Day 9 in the Phase III STEMI study.

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

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

3.9 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.

4. Pharmacological Properties

4.1 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)/Intemational Normalised Ratio (INR) tests in plasma, nor bleeding time or fibrinolytic activity.

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.

4.2 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 therapeutics 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.

Hepatic impairment
Fondaparinux pharmacokinetics have not been studied in patients with hepatic impairment.

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).*

4.3 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.

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 apperent 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 ST segment elevation myocardial infarction (STEMI)
OASIS 6 was a double blind, randomised study assessing the safety and efficacy of fondaparinux 2.5 mg once daily, versus usual care (placebo (47%) or UFH (53%) in approximately 12,000 patients with STEMI. All patients received standard treatments for STEMI, including primary PCI (31 %), thrombolytics (45%) or no reperfusion (24%). Of the patients treated with a thrombolytic, 84% were treated with a non-fibrin specific gagent (primarily streptokinase). The mean treatment duration was 6.2 days on fondaparinux. The mean age of the patients was 61 years, and approximately 40% were at least 65 years old. Approximately 40% and 14% of patients had mild (creatinine clearance ≥50 to <80 ml/min) or moderate (creatinine clearance ≥30 to <50 ml/min) renal impairment, respectively.

The primary adjudicated endpoint was a composite of death and recurrent MI (re-MI) within 30 days of randomisation. The incidence of death/re-MI at Day 30 was significantly reduced from 11.1% for the control group to 9.7% for the fondaparinux group (hazard ratio 0.86, 95% CI, 0.77, 0.96, p = 0.008). In the predefined stratum comparing fondaparinux to placebo (i.e patients treated with nonfibrin specific lytics (77.3%), no reperfusion (22%), fibrin-specific lytics (0.3%), primary PCI (0.4%), the incidence of death/re-MI at Day 30 was significantly reduced from 14.0% on placebo to 11.3% (hazard ratio 0.80, 95% CI, 0.69, 0.93, p = 0.003). In the predefined stratum comparing fondaparinux to UFH (patients treated with primary PCI (58.5%), fibrin-specific lytics (13%), non-fibrin-specific lytics (2.6%), and no reperfusion (25.9%), the effects of fondaparinux and UFH on the incidence of death/re-MI at Day 30 were not statistically different: respectively, 8.3% vs 8.7% (hazard ratio 0.94, 95% CI, 0.79, 1.11 p = 0.460). However, in this stratum, in the subgroup of indicated population undergoing thrombolysis or no reperfusion (i.e patients not undergoing primary PCI), the incidence of death/re-MI at Day 30 was significantly reduced from 14.3% on UFH to 11.5% with fondaparinux (hazard ratio 0.79, 95% CI, 0.64, 0.98, p = 0.03).

The incidence of all cause mortality at Day 30 was also significantly reduced from 8.9% for the control group to 7.8% in the fondaparinux group (hazard ratio 0.87, 95% CI, 0.77; 0.98, p

= 0.02). The difference in mortality was statistically significant in stratum 1 (placebo comparator) but not in stratum 2 (UFH comparator). The mortality benefit shown in the fondaparinux group was maintained until the end of follow-up at Day 180.

In patients who were revascularised with a thrombolytic, fondaparinux significantly reduced the incidence of death/re-MI at Day 30 from 13.6% for the control group to 10.9% (hazard ratio 0.79, 95% CI, 0.68;0.93, p = 0.003). Among patients initially not reperfused, the incidence of death/re-MI at Day 30 was significantly reduced from 15% for the control group to 12.1% for the fondaparinux group (hazard ratio 0.79, 95% CI, 0.65;0.97, p = 0.023). In patients treated with the primary PCI, the incidence of death/re-MI at Day 30 was not statistically different between the two gropus [6.0% in fondaparinux group vs 4.8% in the control; hazard ratio 1.26, 95% CI, 0.96, 1.66].

By Day 9, 1.1% of patients treated with fondaparinux and 1.4% of control patients experienced a severe haemorrhage. In patients given a thrombolytic, severe haemorrhage occurred in 1.3% of the fondaparinux patients and in 2.0% of controls. In patients initially not reperfused, the incidence of severe haemorrhage was 1.2% for fondaparinux vs 1.5% for controls. For patients receiving primary PCI, the incidence of severe haemorrhage was 1.0% for fondaparinux and 0.4% for controls.

The efficacy findings and results on severe haemorrhage were consistent across prespecified subgroups such as elderly, renally impaired patients, type of concomitant platelet aggregation inhibitors aspirin, thienopyridines).

4.4 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.

5. Pharmaceutical particulars

5.1 List of Excipients

Sodium chloride

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

5.2 Incompatibilities

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

5.3 Shelf Life

36 months.
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.

5.4 Special Precautions for Storage

Do not freeze. Store below 25°C.

5.5 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™ 2.5mg/0.5ml, 5.0mg/0.4ml, 7.5mg/0.6ml, 10mg/0.8ml are available in pack sizes of 2 and 10 pre-filled syringes with a blue plunger and an automatic safety system.

5.6 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 injections.

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 50 ml) 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.

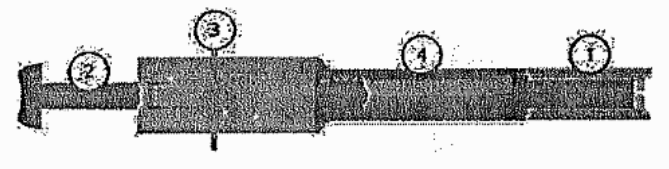
Instruction for self-administration by subcutaneous injection is included in the package leaflet.

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:

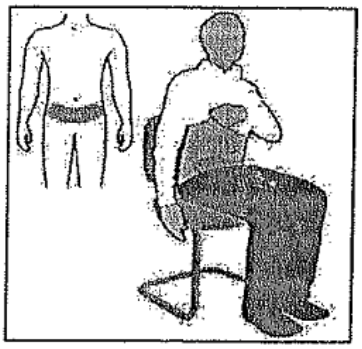
① Needle guard
② Plunger
③ Finger-grip
④ Security sleeve



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).**



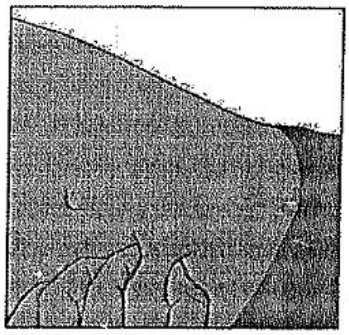
Picture A

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.

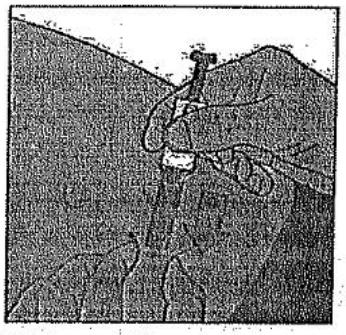
4. Clean the injection area with an alcohol wipe.

5. Gently pinch the skin that has been cleaned to make a fold. Hold the fold between the thumb and the forefinger during the entire injection **(picture B)**.



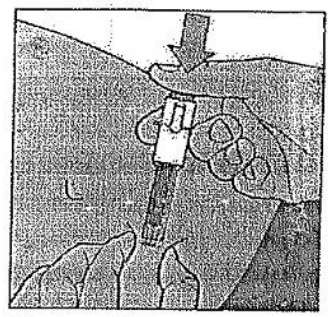
Picture B

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



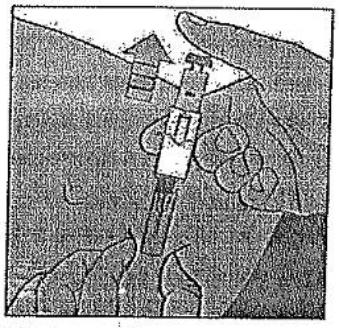
Picture C

7. Inject ALL of the contents of the syringe by pressing down on the plunger as far as it goes.
(picture D).



Picture D

8. 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 E)**.



Picture E

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

ARIXTRA™ is a trademark of the GlaxoSmithKline group of companies.

HARUS DENGAN RESEP DOKTER

Arixtra Injection 7.5mg/0.6ml	Reg. No. DKI1285100443B1
Arixtra Injection 10.0mg/0.8ml	Reg. No. DKI1285100443B1

Manufactured by
Glaxo Wellcome Production, France

Imported by
PT. Glaxo Wellcome Indonesia
Jakarta, Indonesia

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gsk GlaxoSmithKline