1. NAME OF THE MEDICINAL PRODUCT

Arixtra 2.5 mg/0.5 ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe (0.5 ml) contains 2.5 mg of fondaparinux sodium.

Excipient(s) with known effect: Contains less than 1 mmol of sodium (23 mg) per dose, and therefore is essentially sodium free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.
The solution is a clear and colourless liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Prevention of Venous Thromboembolic Events (VTE) in adults undergoing major orthopaedic surgery of the lower limbs such as hip fracture, major knee surgery or hip replacement surgery.

Prevention of Venous Thromboembolic Events (VTE) in adults undergoing abdominal surgery who are judged to be at high risk of thromboembolic complications, such as patients undergoing abdominal cancer surgery (see section 5.1).

Prevention of Venous Thromboembolic Events (VTE) in adult medical patients who are judged to be at high risk for VTE and who are immobilised due to acute illness such as cardiac insufficiency and/or acute respiratory disorders, and/or acute infectious or inflammatory disease.

Treatment of unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI) in adults for whom urgent (< 120 mins) invasive management (PCI) is not indicated (see sections 4.4 and 5.1).

Treatment of ST segment elevation myocardial infarction (STEMI) in adults who are managed with thrombolytics or who initially are to receive no other form of reperfusion therapy.

4.2 Posology and method of administration

Posology
Patients undergoing major orthopaedic or abdominal surgery
The recommended dose of fondaparinux is 2.5 mg once daily administered post-operatively by subcutaneous injection.

The initial dose should be given 6 hours following surgical closure provided that haemostasis has been established.

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 fondaparinux should be considered for up to an additional 24 days (see section 5.1).

Medical patients who are at high risk for thromboembolic complications based on an individual risk assessment
The recommended dose of fondaparinux is 2.5 mg once daily administered by subcutaneous injection. A treatment duration of 6-14 days has been clinically studied in medical patients (see section 5.1).

Treatment of unstable angina/non- ST segment elevation myocardial infarction (UA/NSTEMI)
The recommended dose of fondaparinux is 2.5 mg once daily, administered by subcutaneous injection. Treatment should be initiated as soon as possible following diagnosis and continued for up to a maximum of 8 days or until hospital discharge if that occurs earlier.

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

Treatment of ST segment elevation myocardial infarction (STEMI)
The recommended dose of fondaparinux is 2.5 mg once daily. The first dose of fondaparinux is administered intravenously and subsequent doses are administered by subcutaneous injection. Treatment should be initiated as soon as possible following diagnosis and continued for up to a maximum of 8 days or until hospital discharge if that occurs earlier.

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

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

<u>*Special populations*</u>

Prevention of VTE following Surgery
In patients undergoing surgery, timing of the first fondaparinux injection requires strict adherence in patients ≥75 years, and/or with body weight <50 kg and/or with renal impairment with creatinine clearance ranging between 20 to 50 ml/min.

The first fondaparinux administration should be given not earlier than 6 hours following surgical closure. The injection should not be given unless haemostasis has been established (see section 4.4).

Renal impairment
- *Prophylaxis of VTE* –Fondaparinux should not be used in patients with creatinine clearance <20 ml/min (see section 4.3). Arixtra 2.5mg/0.6ml should not be used in patients with creatinine clearance in the range of 20 to 50 ml/min because adequate dosage reduction cannot be achieved (see sections 4.4 and 5.2). No dosage reduction is required for patients with mild renal impairment (creatinine clearance >50 ml/min).

- *Treatment of UA/NSTEMI and* STEMI - Fondaparinux should not be used in patients with creatinine clearance < 20 ml/min (see section 4.3). No dosage reduction is required for patients with creatinine clearance > 20 ml/min.

Hepatic impairment
Prevention of VTE and Treatment of UA/NSTEMI and STEMI - No dosing adjustment is necessary in patients with either mild or moderate hepatic impairment. In patients with severe hepatic impairment, fondaparinux should be used with care as this patient group has not been studied (see sections 4.4 and 5.2).

Paediatric population - Fondaparinux is not recommended for use in children below 17 years of age due to a lack of data on safety and efficacy.

Low body weight
Prevention of VTE and treatment of UA/NSTEMI and STEMI – Patients with body weight<50 kg are at increased risk of bleeding. Elimination of fondaparinux decreases with weight. Fondaparinux should be used with caution in these patients (see section 4.4).

Method of administration

- *Subcutaneous administration*
  Fondaparinux is administered by deep subcutaneous injection while the patient is lying down. Sites of administration 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.

- *Intravenous administration (first dose in patients with STEMI 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 minibag, the infusion should be given over 1 to 2 minutes.

For additional instructions for use and handling and disposal see section 6.6.

4.3 Contraindications

- hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- active clinically significant bleeding
- acute bacterial endocarditis
- severe renal impairment defined by creatinine clearance < 20 ml/min.

4.4 Special warnings and precautions for use

Fondaparinux must not be administered intramuscularly.

Haemorrhage
Fondaparinux should be used with caution in patients who have an increased risk of haemorrhage, such as those with congenital or acquired bleeding disorders (e.g. platelet count <50,000/mm^3), active ulcerative gastrointestinal disease and recent intracranial haemorrhage or shortly after brain, spinal or ophthalmic surgery and in special patient groups as outlined below.

For prevention of VTE- 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). When required, concomitant therapy with vitamin K antagonist should be administered in accordance with the information of section 4.5. 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.

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

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

In UA/NSTEMI and STEMI patients undergoing non-primary PCI, the use of fondaparinux as the sole anticoagulant during PCI is not recommended due to an increased risk of guiding catheter thrombus (see clinical studies section 5.1). Therefore adjunctive UFH should be used during non-primary PCI according to standard practice (see posology in section 4.2).

Spinal / Epidural anaesthesia
In patients undergoing major orthopaedic surgery, epidural or spinal haematomas that may result in long-term or permanent paralysis cannot be excluded with the concurrent use of fondaparinux 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 is generally decreasing with age, elderly patients may show reduced elimination and increased exposure of fondaparinux (see section 5.2). Fondaparinux should be used with caution in elderly patients (see section 4.2).

Low body weight:
Prevention of VTE and Treatment of UA/NSTEMI and STEMI - Patients with body weight <50 kg are at increased risk of bleeding. Elimination of fondaparinux decreases with weight. Fondaparinux should be used with caution in these patients. (See section 4.2).

Renal impairment
Fondaparinux is known to be mainly excreted by the kidney.

- *Prophylaxis of VTE* - Patients with creatinine clearance <50 ml/min are at increased risk of bleeding and VTE and should be treated with caution (see sections 4.2, 4.3 and 5.2). There are limited clinical data available from patients with creatinine clearance less than 30 ml/min.

- *Treatment of UA/NSTEMI and* STEMI - For the treatment of UA/NSTEMI and STEMI, there are limited clinical data available on the use of fondaparinux 2.5mg once daily in patients with creatinine clearance between 20 and 30 ml/min. Therefore the physician should determine if the benefit of treatment outweighs the risk (see sections 4.2 and 4.3).

Severe hepatic impairment:
Prevention of VTE and Treatment of UA/NSTEMI and STEMI - Dosing adjustment of fondaparinux is not necessary. However, the use of fondaparinux should be considered with caution because of an

increased risk of bleeding due to a deficiency of coagulation factors in patients with severe hepatic impairment (see section 4.2).

Patients with Heparin Induced Thrombocytopenia
Fondaparinux should be used with caution in patients with a history of HIT. The efficacy and safety of fondaparinux have not been formally studied in patients with HIT type II. Fondaparinux does not bind to platelet factor 4 and does not usually cross-react with sera from patients with Heparin Induced Thrombocytopenia (HIT) type II. However, rare spontaneous reports of HIT in patients treated with fondaparinux have been received.

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

4.5 Interaction with other medicinal products and other forms of interaction

Bleeding risk is increased with concomitant administration of fondaparinux and agents that may enhance the risk of haemorrhage (see section 4.4).

Oral anticoagulants (warfarin), platelet inhibitors (acetylsalicylic acid), NSAIDs (piroxicam) and digoxin did not interact with the pharmacokinetics of fondaparinux. The fondaparinux dose (10 mg) in the interaction studies was higher than the dose recommended for the present indications. Fondaparinux neither influenced the INR activity of warfarin, nor the bleeding time under acetylsalicylic acid or piroxicam treatment, nor the pharmacokinetics 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 antagonist is required, treatment with fondaparinux should be continued until the target INR value has been reached.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of fondaparinux in pregnant women. Animal studies are insufficient with respect to effects on pregnancy, embryo/foetal development, parturition and postnatal development because of limited exposure. Fondaparinux should not be prescribed to pregnant women unless clearly necessary.

Breast-feeding
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 fondaparinux. Oral absorption by the child is however unlikely.

Fertility
There are no data available on the effect of fondaparinux on human fertility. Animal studies do not show any effect on fertility.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The most commonly reported serious adverse reactions reported with fondaparinux are bleeding complications (various sites including rare cases of intracranial/ intracerebral and retroperitoneal bleedings) and anaemia. Fondaparinux should be used with caution in patients who have an increased risk of haemorrhage (see section 4.4).

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
- 1,407 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.
- 2,517 patients treated for Venous Thrombo-Embolism and treated with fondaparinux for an average of 7 days (Arixtra 7.5 mg/0.6 ml).

These adverse reactions should be interpreted within the surgical and medical context of the indications. The adverse event profile reported in the ACS program is consistent with the adverse drug reactions identified for VTE prophylaxis.
Adverse reactions are listed below by system organ class and frequency. 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).

System organ class **MedDRA**	**common** **(≥ 1/100, <1/10)**	**uncommon** **(≥ 1/1,000, <1/100)**	**rare** **(≥ 1/10,000, <1/1,000)**
Infections and infestations			post-operative wound infections
Blood and lymphatic system disorders	Anaemia, post-operative haemorrhage, uterovaginal haemorrhage*, haemoptysis, haematuria, haematoma, gingival bleeding, purpura, epistaxis, gastrointestinal bleeding, hemarthrosis*, ocular bleeding*, bruise*	thrombocytopenia, thrombocythaemia, platelet abnormal, coagulation disorder	retroperitoneal bleeding*, hepatic, intracranial/ intracerebral bleeding*
Immune system disorders			allergic reaction (including very rare reports of angioedema, anaphylactoid/ anaphylactic reaction)
Metabolism and nutrition disorders			hypokalaemia, non-protein-nitrogen (Npn) increased[1]*
Nervous system disorders		headache	anxiety, confusion, dizziness, somnolence, vertigo

System organ class **MedDRA**	**common** **(≥ 1/100, <1/10)**	**uncommon** **(≥ 1/1,000, <1/100)**	**rare** **(≥ 1/10,000, <1/1,000)**
Vascular disorders			hypotension
Respiratory, thoracic and mediastinal disorders		dyspnoea	coughing
Gastrointestinal disorders		nausea, vomiting	abdominal pain, dyspepsia, gastritis, constipation, diarrhoea
Hepatobiliary disorders		abnormal liver function tests, hepatic enzymes increased	bilirubinaemia
Skin and subcutaneous tissue disorders		rash erythematous, pruritus	
General disorders and administration site conditions		oedema, oedema peripheral, pain, fever, chest pain, wound secretion	reaction at injection site, leg pain, fatigue, flushing, syncope, hot flushes, oedema genital

(1) Npn stands for non-protein-nitrogen such as urea, uric acid, amino acid, etc.
** ADRs occurred at higher dose 7.5 mg/0.6 ml.*

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

Arixtra 2.5 mg/0.5 ml
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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il
Additionally, you can also report via the following address: Padagis.co.il

4.9 Overdose

Fondaparinux doses above the recommended regimen may lead to an increased risk of bleeding. There is no known antidote to fondaparinux.

Overdose associated with bleeding complications should lead to treatment discontinuation and search for the primary cause. Initiation of appropriate therapy such as surgical haemostasis, blood replacements, fresh plasma transfusion, plasmapheresis should be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antithrombotic agents.
ATC code: B01AX05

Pharmacodynamic effects

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 effects on platelets.

At the 2.5 mg dose, fondaparinux does not affect 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 aPTT prolongation have been received.

Fondaparinux does not usually cross-react with sera from patients with heparin-induced thrombocytopaenia (HIT). However, rare spontaneous reports of HIT in patients treated with fondaparinux have been received.

Clinical studies

Prevention of Venous Thromboembolic Events (VTE) in patients undergoing major orthopaedic surgery of the lower limbs treated up to 9 days
The fondaparinux clinical program was designed to demonstrate the efficacy of fondaparinux for the prevention of venous thromboembolic events (VTE), i.e. proximal and distal deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing major orthopaedic surgery of the lower limbs such as hip fracture, major knee surgery or hip replacement surgery. Over 8,000 patients (hip fracture – 1,711, hip replacement – 5,829, major knee surgery – 1,367) were studied in controlled Phase II and III clinical studies. Fondaparinux 2.5 mg once daily started 6-8 hours postoperatively was compared with enoxaparin 40 mg once daily started 12 hours before surgery, or 30 mg twice daily started 12-24 hours after surgery.

In a pooled analysis of these studies, the recommended dose regimen of fondaparinux versus enoxaparin was associated with a significant decrease (54% [95% CI, 44 %; 63%]) in the rate of VTE evaluated up to day 11 after surgery, irrespective of the type of surgery performed. The majority of endpoint events were diagnosed by a prescheduled venography and 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 2.8% of fondaparinux patients treated with the recommended dose, compared to 2.6% with enoxaparin.

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
In a randomised double-blind clinical trial, 737 patients were treated with fondaparinux 2.5 mg once daily for 7 +/- 1 days following hip fracture surgery. At the end of this period, 656 patients were randomised to receive fondaparinux 2.5 mg once daily or placebo for an additional 21 +/- 2 days. Fondaparinux provided a significant reduction in the overall rate of VTE compared with placebo [3 patients (1.4%) vs 77 patients (35%), respectively]. The majority (70/80) of the recorded VTE events were venographically detected non-symptomatic cases of DVT. Fondaparinux also provided a significant reduction in the rate of symptomatic VTE (DVT, and / or PE) [1 (0.3%) vs 9 (2.7%) patients, respectively] including two fatal PE reported in the placebo group. Major bleedings, all at surgical site and none fatal, were observed in 8 patients (2.4%) treated with fondaparinux 2.5 mg compared to 2 (0.6%) with placebo.

Prevention of Venous Thromboembolic Events (VTE) in patients undergoing abdominal surgery who are judged to be at high risk of thromboembolic complications, such as patients undergoing abdominal cancer surgery
In a double-blind clinical study, 2,927 patients were randomised to receive fondaparinux 2.5mg once daily or dalteparin 5,000 IU once daily, with one 2,500 IU preoperative injection and a first 2,500 IU post-operative injection, for 7$\pm$2 days. The main sites of surgery were colonic/rectal, gastric, hepatic, cholecystectomy or other biliary. Sixty-nine percent of the patients underwent surgery for cancer. Patients under-going urological (other than kidney) or gynaecological surgery, laparoscopic surgery or vascular surgery were not included in the study.

In this study, the incidence of total VTE was 4.6% (47/1,027) with fondaparinux, versus 6.1%: (62/1,021) with dalteparin: odds ratio reduction [95%CI] = -25.8% [-49.7%, 9.5%]. The difference in total VTE rates between the treatment groups, which was not statistically significant, was mainly due to a reduction of asymptomatic distal DVT. The incidence of symptomatic DVT was similar between treatment groups: 6 patients (0.4%) in the fondaparinux group vs 5 patients (0.3%) in the dalteparin group. In the large subgroup of patients undergoing cancer surgery (69% of the patient population), the VTE rate was 4.7% in the fondaparinux group, versus 7.7% in the dalteparin group.

Major bleeding was observed in 3.4% of the patients in the fondaparinux group and in 2.4% of the dalteparin group.

Prevention of Venous Thromboembolic Events (VTE) in medical patients who are at high risk for thromboembolic complications due to restricted mobility during acute illness
In a randomised double-blind clinical trial, 839 patients were treated with fondaparinux 2.5 mg once daily or placebo for 6 to 14 days. This study included acutely ill medical patients, aged $\geq$ 60 years, expected to require bed rest for at least four days, and hospitalized for congestive heart failure NYHA class III/IV and/or acute respiratory illness and/or acute infectious or inflammatory disease. Fondaparinux significantly reduced the overall rate of VTE compared to placebo [18 patients (5.6%) vs 34 patients (10.5%), respectively]. The majority of events were asymptomatic distal DVT. Fondaparinux also significantly reduced the rate of adjudicated fatal PE [0 patients (0.0%) vs 5 patients (1.2%), respectively]. Major bleedings were observed in 1 patient (0.2%) of each group.

Treatment of unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI)
OASIS 5 was a double-blind, randomised, non-inferiority study with fondaparinux 2.5 mg subcutaneously once daily versus enoxaparin 1 mg/kg subcutaneously twice daily in approximately 20,000 patients with UA/NSTEMI. All patients received standard medical treatment for UA/NSTEMI, with 34% of patients undergoing PCI and 9% undergoing CABG. The mean treatment duration was 5.5 days in the fondaparinux group and 5.2 days in the enoxaparin group. If PCI was performed, patients received either intravenous fondaparinux (fondaparinux patients) or weight adjusted

intravenous UFH (enoxaparin patients) as adjunctive therapy, dependent on the timing of the last subcutaneous dose and planned use of GP IIb/IIIa inhibitor. The mean age of the patients was 67 years, and approximately 60% were at least 65 years old. Approximately 40% and 17% of patients had mild (creatinine clearance ≥50 to <80 ml/min) or moderate (creatinine clearance ≥30 to <50 ml/min) renal impairment, respectively.

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

By Day 30, the incidence of all cause mortality was significantly reduced from 3.5% on enoxaparin to 2.9% on fondaparinux (hazard ratio 0.83, 95% CI, 0.71;0.97, p = 0.02). The effects on the incidence of MI and RI were not statistically different between the fondaparinux and enoxaparin treatment groups.

At Day 9 the incidence of major bleeding on fondaparinux and enoxaparin was 2.1% and 4.1%, respectively (hazard ratio 0.52, 95% CI, 0.44;0.61, p < 0.001).

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

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

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

In a study of 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. In subjects randomized to the “standard dose UFH” or the “low dose UFH” regimen the median dose of UFH was 85 U/kg and 50 U/kg, respectively.

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

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 adjudicated guiding catheter thrombus were 0.1% (1/1002) and 0.5% (5/1024), in patients randomised to "standard dose" and "low dose" UFH respectively during PCI.
Four (0.3%) non-randomised patients experienced thrombus in the diagnostic catheter during coronary angiography. 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)
OASIS 6 was a double blind, randomised study assessing the safety and efficacy of fondaparinux 2.5 mg once daily, versus usual care (placebo (47%) or UFH (53%) in approximately 12,000 patients with STEMI. All patients received standard treatments for STEMI, including primary PCI (31%), thrombolytics (45%) or no reperfusion (24%). Of the patients treated with a thrombolytic, 84% were treated with a non-fibrin specific agent (primarily streptokinase). The mean treatment duration was 6.2 days on fondaparinux. The mean age of the patients was 61 years, and approximately 40% were at least 65 years old. Approximately 40% and 14% of patients had mild (creatinine clearance ≥50 to <80 ml/min) or moderate (creatinine clearance ≥30 to <50 ml/min) renal impairment, respectively.

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 non-fibrin 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 primary PCI, the incidence of death/re-MI at Day 30 was not statistically different between the two groups [6.0% in fondaparinux group vs 4.8% in the control group; 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.

In subjects undergoing primary PCI the incidence of adjudicated guiding catheter thrombus was 1.2% vs 0% in fondaparinux vs. control subjects, respectively.

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

5.2 Pharmacokinetic properties

Absorption
After subcutaneous dosing, fondaparinux is completely and rapidly absorbed (absolute bioavailability 100%). Following a single subcutaneous injection of fondaparinux 2.5 mg to young healthy subjects, peak plasma concentration (mean C_{max} = 0.34 mg/l) is obtained 2 hours post-dosing. Plasma concentrations of half the mean C_{max} values are reached 25 minutes post-dosing.

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.

Mean (CV%) steady state pharmacokinetic parameters estimates of fondaparinux in patients undergoing hip replacement surgery receiving fondaparinux 2.5 mg once daily are: C_{max} (mg/l) - 0.39 (31%), T_{max} (h) - 2.8 (18%) and C_{min} (mg/l) -0.14 (56%). In hip fracture patients, associated with their increased age, fondaparinux steady state plasma concentrations are: C_{max} (mg/l) - 0.50 (32%), C_{min} (mg/l) - 0.19 (58%).

Distribution
The distribution volume of fondaparinux is limited (7-11 litres). *In vitro*, fondaparinux is highly and specifically bound to antithrombin protein with a dose-dependant plasma concentration binding (98.6% to 97.0% in the concentration range from 0.5 to 2 mg/l). Fondaparinux does not bind significantly to other plasma proteins, including platelet factor 4 (PF4).

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

Biotransformation
Although not fully evaluated, there is no evidence of fondaparinux metabolism and in particular no evidence for the formation of active metabolites.

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

Elimination
The elimination half-life ($t_{½}$) is about 17 hours in healthy young subjects and about 21 hours in healthy elderly subjects. Fondaparinux is excreted to 64 – 77 % by the kidney as unchanged compound.

Special populations

Paediatric patients - Fondaparinux has not been investigated in this population for the prevention of VTE or acute coronary syndrome (ACS).

Elderly patients - Renal function may decrease with age and thus, the elimination capacity for fondaparinux may be reduced in elderly. In patients >75 years undergoing orthopaedic surgery, the estimated plasma clearance was 1.2 to 1.4 times lower than in patients <65 years.

Renal impairment - Compared with patients with normal renal function (creatinine clearance > 80 ml/min), plasma clearance is 1.2 to 1.4 times lower in patients with mild renal impairment (creatinine clearance 50 to 80 ml/min) and on average 2 times lower in patients with moderate renal impairment (creatinine clearance 30 to 50 ml/min). In severe renal impairment (creatinine clearance < 30 ml/min), plasma clearance is approximately 5 times lower than in normal renal function. Associated terminal half-life values were 29 h in moderate and 72 h in patients with severe renal impairment.

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

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

Body weight - Plasma clearance of fondaparinux increases with body weight (9% increase per 10 kg).

Hepatic impairment - Following a single, subcutaneous dose of fondaparinux in subjects with moderate hepatic impairment (Child-Pugh Category B), total (i.e., bound and unbound) 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. Consequently, 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.

The pharmacokinetics of fondaparinux has not been studied in patients with severe hepatic impairment (see sections 4.2 and 4.4).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, and genotoxicity. Animal studies are insufficient with respect to effects on toxicity to reproduction because of limited exposure.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Water for injection
Sodium hydroxide
Hydrochloric acid

6.2 Incompatibilities

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

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

If fondaparinux sodium 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.

6.4 Special precautions for storage

Store below 25°C. Do not freeze.

6.5 Nature and contents of container

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

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

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

Instruction on self-administration by subcutaneous injection is included in the Package Leaflet.

The needle protection system of the Arixtra pre-filled syringes have been designed with a safety system to protect from needle stick injuries following injection.

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

7**. Manufacturer:**

Aspen Notre Dame De Bondeville, Notre Dame De Bondeville, France

8. **Registration Holder:**

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9. **Registration Number:**

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