1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ARIXTRA 2,5 mg/0,5 ml solution for injection - Pre-filled syringes

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled syringe of ARIXTRA 2,5 mg/0,5 ml contains 2,5 mg of fondaparinux sodium in 0,5 ml of an isotonic solution.

Sugar free

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection - Pre-filled syringes

ARIXTRA 2,5 mg/0,5 ml is in a pre-filled glass syringe containing a clear to practically clear and colourless solution, free from visible particles.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

ARIXTRA 2,5 mg/0,5 ml is indicated in adults:

- To reduce the risk of venous thromboembolic events (VTE) in patients undergoing major orthopaedic surgery of the lower limbs such as hip fracture, major knee surgery or hip replacement surgery.

- To reduce the risk of venous thromboembolic events (VTE) in patients undergoing abdominal surgery who are at risk of thromboembolic complications.
- For the treatment of unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI) acute coronary syndrome for the prevention of death, myocardial infarction and refractory ischaemia. ARIXTRA 2,5 mg/0,5 ml has been shown to reduce all-cause mortality in patients with UA/NSTEMI.
- For the treatment of ST segment elevation myocardial infarction (STEMI) acute coronary syndrome for the prevention of death and myocardial re-infarction in patients who are managed with thrombolytics or who initially are to receive no other form of reperfusion therapy. ARIXTRA 2,5 mg/0,5 ml has been shown to reduce all-cause mortality in patients with STEMI.
- To reduce the risk of venous thromboembolic events (VTE) in medical patients who are at risk of thromboembolic complications due to restricted mobility during acute illness such as cardiac insufficiency and/or acute respiratory disorders, and/or acute infectious or inflammatory disease.

4.2. Posology and method of administration

Posology

Adults

Orthopaedic and abdominal surgery:

The recommended dose of ARIXTRA 2,5 mg/0,5 ml is 2,5 mg once daily administered post-operatively by subcutaneous injection.

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

Treatment should be continued for at least 7±2 days and for as long as the risk of VTE persists.

Treatment of Unstable Angina/Non-ST Segment Elevation Myocardial Infarction (UA/NSTEMI):

The recommended dose of ARIXTRA 2,5 mg/0,5 ml 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 2,5 mg/0,5 ml , ARIXTRA 2,5 mg/0,5 ml should be stopped and 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 2,5 mg/0,5 ml (see section 4.4).

The timing of restarting subcutaneous ARIXTRA 2,5 mg/0,5 ml after sheath removal should be based on clinical judgement. In the UA/NSTEMI clinical trial, treatment with ARIXTRA 2,5 mg/0,5 ml was restarted no earlier than 2 hours after sheath removal.

In patients who are to undergo coronary artery bypass graft (CABG) surgery, ARIXTRA 2,5 mg/0,5 ml 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 2,5 mg/0,5 ml is 2,5 mg once daily. The first dose of ARIXTRA 2,5 mg/0,5 ml 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 2,5 mg/0,5 ml , ARIXTRA 2,5 mg/0,5 ml should be stopped and 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 2,5 mg/0,5 ml (see section 4.4

The timing of restarting subcutaneous ARIXTRA 2,5 mg/0,5 ml after sheath removal should be based on clinical judgment. In the STEMI clinical trial treatment with ARIXTRA 2,5 mg/0,5 ml was restarted no earlier than 3 hours after sheath removal.

In patients who are to undergo coronary artery bypass graft (CABG) surgery, ARIXTRA 2,5 mg/0,5 ml should not be given during the 24 hours before surgery and may be restarted 48 hours post-operatively.

ARIXTRA 2,5 mg/0,5 ml is administered by subcutaneous or intravenous injection. It must NOT be administered by intramuscular injection.

Medical patients at risk of thromboembolic complications

The recommended dose of ARIXTRA 2,5 mg/0,5 ml 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.

Special populations

Elderly

No dosing adjustment is necessary. In elderly patients, ARIXTRA 2,5 mg/0,5 ml should be used with care, including strict adherence to the timing of the first dose (see section 4.4),

Renal impairment

Prevention of VTE: No dosage reduction is required in patients with a creatinine clearance greater than or equal to 30 ml /min (see section 4.4).

In patients with a creatinine clearance of between 20 to 30 ml /min in whom the medical practitioner determines that the benefit of thromboprophylaxis exceeds the risk, a dose 2,5 mg on alternate days (each dose approximately 48 hours apart) is recommended (see section 4.4 and 5.2).

ARIXTRA 2,5 mg/0,5 ml is not recommended for use in patients with a creatinine clearance of less than 20 ml /min (see section 4.3). In patients undergoing surgery, the timing of the first dose of ARIXTRA 2,5 mg/0,5 ml requires strict adherence.

Treatment of UA/NSTEMI and STEMI: ARIXTRA 2,5 mg/0,5 ml is not recommended for use in patients with a creatinine clearance of less than 20 ml /min (see section 4.3). No dosage reduction is required for patients with a creatinine clearance greater than or equal to 20 ml /min (see section 4.4).

Hepatic impairment

No dosing adjustment is necessary in patients with mild to moderate hepatic impairment (see section 5.2). In patients with severe hepatic impairment, ARIXTRA 2,5 mg/0,5 ml should be used with caution (see section 4.4).

Patients with body weight < 50 kg

ARIXTRA 2,5 mg/0,5 ml should not be used (see section 4.3).

Paediatric population

The safety and efficacy of ARIXTRA 2,5 mg/0,5 ml in patients under the age of 18 years has not been studied.

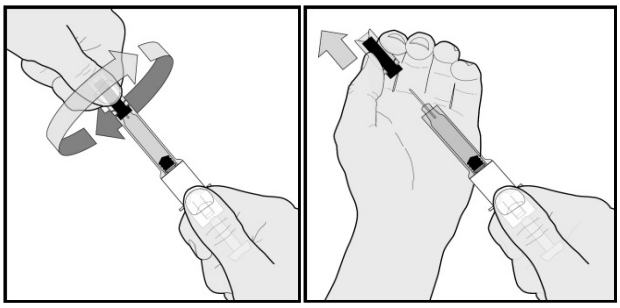
Method of administration

Subcutaneous administration

ARIXTRA 2,5 mg/0,5 ml is administered by subcutaneous or intravenous injection. It must NOT be administered by intramuscular injection.

ARIXTRA 2,5 mg/0,5 ml is intended for use under a medical practitioner's guidance. Patients may self-inject only if their medical practitioner 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 patient information leaflet.

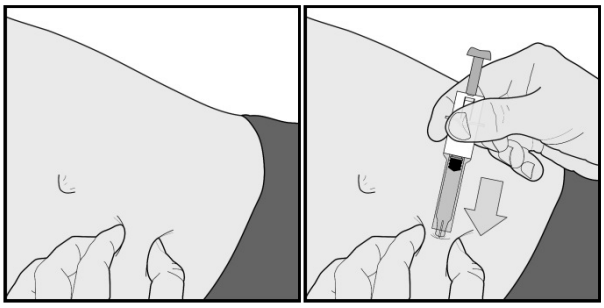
To use the ARIXTRA 2,5 mg/0,5 ml syringes, remove the rigid needle shield by turning and pulling it



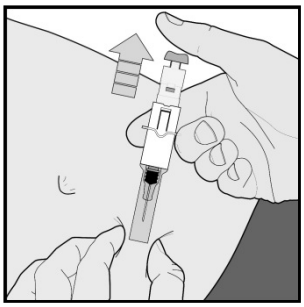
To avoid the loss of medicine when using the pre-filled syringe do not expel the air bubble from the syringe before the injection.

Administration should be made in fatty tissues alternating injection sites (e.g., alternating between the left and right anterolateral or the left and right posterolateral abdominal wall).

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 and the plunger should be completely depressed.



When the injection is finished, the plunger should be released. The plunger rises automatically while the needle withdraws from the skin and retracts into the sleeve.



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 % sodium chloride mini-bag. To avoid the loss of medicine 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 medicine is administered. If administered via a mini-bag, the infusion should be given over 1 to 2 minutes.

If ARIXTRA 2,5 mg/0,5 ml is added to a 0,9 % sodium chloride mini-bag it should ideally be infused immediately but can be stored at room temperature for up to 24 hours.

Instructions for use

The subcutaneous injection is administered in the same way as with a classical syringe (see section 6.6).

Parenteral medicines should be inspected visually for visible particles and discolouration prior to administration (see section 6.6).

4.3 Contraindications

ARIXTRA 2,5 mg/0,5 ml is contraindicated in :

- Patients with hypersensitivity to fondaparinux or to any excipients in ARIXTRA 2,5 mg/0,5 ml (see section 6.1).
- Active major bleeding.
- Severe renal impairment (creatinine clearance < 20 ml /min).
- Infective endocarditis.
- Pregnancy and lactation (see section 4.6).
- Patients with body weight less than 50 kg.

ARIXTRA 2,5 mg/0,5 ml should not be given to patients who have undergone surgery of the brain, eye, ear or spinal cord or who have injuries of the brain, eye, ear or spinal cord.

4.4. Special warnings and precautions for use

Spinal/epidural anaesthesia

Epidural or spinal haematomas which may result in long-term or permanent paralysis cannot be excluded with the concurrent use of ARIXTRA 2,5 mg/0,5 ml and spinal/epidural anaesthesia or spinal puncture. The risk of these events may be higher with post-operative use of indwelling epidural catheters or the concomitant use of other medicines affecting haemostasis, including NSAID, acetylsalicylic acid and other platelet inhibitors. Epidural and spinal catheters should be removed at the end of surgical procedures.

ARIXTRA 2,5 mg/0,5 ml is not intended for intramuscular administration.

ARIXTRA 2,5 mg/0,5 ml cannot be used interchangeably (unit for unit) with heparin, low molecular weight heparins or heparinoids, as they differ in anti-Xa and anti-IIa activity, units, and dosage. Each of these medicines has its own instructions for use.

Percutaneous coronary intervention (PCI) and risk of guiding catheter thrombus

Clinical trials have shown an increased risk of guiding catheter thrombus in patients treated solely with ARIXTRA 2,5 mg/0,5 ml for anticoagulation during PCI compared to control.

Renal impairment

The plasma clearance of ARIXTRA 2,5 mg/0,5 ml decreases with the severity of renal impairment and is associated with an increased risk of haemorrhage.
Patients with renal impairment, particularly those with a creatinine clearance of less than 30 ml /min are at increased risk of both major bleeding episodes and VTE (see section 4.3).

Prevention of VTE: There are limited clinical data available for the use of ARIXTRA 2,5 mg/0,5 ml for prevention of VTE in patients with creatinine clearance less than 20 ml /min. Therefore, ARIXTRA 2,5 mg/0,5 ml is not recommended for prevention of VTE in these patients (see section 4.2, 4.3 and 5.2).

Medicines that may enhance the risk of haemorrhage should not be administered concomitantly with fondaparinux. These medicines include desirudin, fibrinolytic medicines 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 medicines (acetylsalicylic acid, dipyridamole, sulfinpyrazone, ticlopidine or clopidogrel), and NSAIDs should be used with caution. If co-administration is essential, close monitoring is necessary (see section 4.5).

Prevention of VTE following surgery (timing of first ARIXTRA 2,5 mg/0,5 ml 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: There are limited clinical data available for the use of ARIXTRA 2,5 mg/0,5 ml for the treatment of UA/NSTEMI and STEMI in patients with creatinine

clearance between 20 to 30 ml /min. Therefore, the medical practitioner should determine if the benefit of treatment outweighs the risk (see section 4.2 and section 5.2). ARIXTRA 2,5 mg/0,5 ml is not recommended in patients with a creatinine clearance of less than 20 ml /min (see section 4.3).

Treatment of UA/NSTEMI and STEMI: ARIXTRA 2,5 mg/0,5 ml should be used with caution in patients who are being treated concomitantly with other medicines that increase the risk of haemorrhage (such as GPIIb/IIIa inhibitors or thrombolytics).

Renal function should be assessed periodically in patients receiving ARIXTRA 2,5 mg/0,5 ml. ARIXTRA 2,5 mg/0,5 ml should be discontinued immediately in patients who develop severe renal impairment or labile renal function while on therapy. After discontinuation of ARIXTRA 2,5 mg/0,5 ml, its anticoagulant effects may persist for 2 to 4 days in patients with normal renal function (i.e. at least 3 to 5 half-lives). The anticoagulant effects of ARIXTRA 2,5 mg/0,5 ml may persist even longer in patients with renal impairment (see section 5.2).

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 fondaparinux. ARIXTRA 2,5 mg/0,5 ml should be used with caution in elderly patients (see section 4.2).

Low body weight:

- Patients with body weight less than 50 kg are at increased risk of bleeding. Elimination of fondaparinux decreases with weight decrease. For prophylaxis following surgery, ARIXTRA 2,5 mg/0,5 ml should be used with caution in these patients (see sections 4.2 and 4.3).

Severe hepatic impairment

In patients with an elevation in prothrombin time, the use of ARIXTRA 2,5 mg/0,5 ml 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 section 4.2).

Haemorrhage

ARIXTRA 2,5 mg/0,5 ml Injection, like other coagulants, should be used with extreme caution in conditions with increased risk of haemorrhage, such as congenital or acquired bleeding disorders, active ulcerative and angiodysplastic gastrointestinal disease, haemorrhagic stroke or intracranial haemorrhage, or shortly after brain, spinal, or ophthalmological surgery, or in patients treated concomitantly with platelet inhibitors.

Laboratory testing

Because routine coagulation tests such as prothrombin time (PT), International Normalised Ratio (INR) and activated partial thromboplastin time (aPTT) are insensitive measures of ARIXTRA 2,5 mg/0,5 ml activity and international standards of heparin or LMWH are not calibrators to measure anti-Factor Xa activity of ARIXTRA 2,5 mg/0,5 ml , if during ARIXTRA 2,5 mg/0,5 ml therapy unexpected changes in coagulation parameters or major bleeding occurs, ARIXTRA 2,5 mg/0,5 ml should be discontinued.

Spinal/epidural anaesthesia

Spinal or epidural haematomas, which may result in long-term or permanent paralysis, can occur with the use of anticoagulants and neuraxial (spinal/epidural) anaesthesia or spinal puncture. The risk of these events may be higher with post-operative use of indwelling epidural catheters or concomitant use of other medicines affecting haemostasis such as NSAIDs.

Thrombocytopenia

Thrombocytopenia can occur with the administration of ARIXTRA 2,5 mg/0,5 ml. Moderate thrombocytopenia (platelet counts between 100 000/mm^3 and 50 000/mm^3) occurred in 2,9 % in patients given ARIXTRA 2,5 mg/0,5 ml 2,5 mg in clinical trials. Severe thrombocytopenia (platelet counts less than 50 000/mm^3) occurred at a rate of 0,2 % in patients given ARIXTRA 2,5 mg/0,5 ml 2,5 mg in clinical trials. Thrombocytopenia of any degree should be monitored closely. If the platelet count falls below 100 000/mm^3, ARIXTRA 2,5 mg/0,5 ml should be discontinued.

Heparin induced thrombocytopenia

ARIXTRA 2,5 mg/0,5 ml 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 2,5 mg/0,5 ml have not been studied in HIT-type II.

Spontaneous reports of HIT in patients treated with ARIXTRA 2,5 mg/0,5 ml have been received. A causal association between treatment with ARIXTRA 2,5 mg/0,5 ml and the occurrence of HIT has not been established.

Latex allergy

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

Paediatric population

The safety and efficacy of ARIXTRA 2,5 mg/0,5 ml in patients under the age of 18 years has not been studied (see section 4.2).

4.5. Interaction with other medicines and other forms of interaction

In clinical studies performed with ARIXTRA 2,5 mg/0,5 ml, the concomitant use of oral warfarin, platelet inhibitors (acetylsalicylic acid), NSAIDs (piroxicam) and digoxin did not interact with the pharmacokinetics/pharmacodynamics of ARIXTRA 2,5 mg/0,5 ml . In addition, ARIXTRA 2,5 mg/0,5 ml neither influenced the pharmacodynamics of warfarin, acetylsalicylic acid, piroxicam and digoxin, nor the pharmacokinetics of digoxin at steady state.

Medicines that may enhance the risk of haemorrhage should be discontinued prior to initiation of ARIXTRA 2,5 mg/0,5 ml therapy. If co-administration is essential, close monitoring may be appropriate.

Since ARIXTRA 2,5 mg/0,5 ml does not inhibit CYP450s (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 or CYP3A4) *in vitro*, ARIXTRA 2,5 mg/0,5 ml is not expected to interact with other medicines *in vivo* by inhibition of CYP-mediated metabolism.

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

4.6. Fertility, pregnancy and lactation

The use of ARIXTRA 2,5 mg/0,5 ml is contraindicated in pregnancy and lactation (see section 4.3).

Pregnancy

There are no adequate data from the use of fondaparinux, as in ARIXTRA 2,5 mg/0,5 ml, in pregnant women. Animal studies are insufficient with respect to effects on pregnancy, embryo/foetal development, parturition and postnatal development because of limited exposure.

Breastfeeding

It is not known whether ARIXTRA 2,5 mg/0,5 ml is excreted in human milk. Breastfeeding is not recommended during treatment with ARIXTRA 2,5 mg/0,5 ml.

Fertility

There are no data available on the effect of fondaparinux, as in ARIXTRA 2,5 mg/0,5 ml, on human fertility.

4.7 Effects on ability to drive and use machines

ARIXTRA 2,5 mg/0,5 ml has a minor influence on a patient's ability to drive and use machines. Since adverse reactions such as dizziness have been reported in patients receiving ARIXTRA 2,5 mg/0,5 ml, patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that ARIXTRA 2,5 mg/0,5 ml does not adversely affect their ability to do so (see section 4.4 and 4.8).

4.8 Undesirable effects

(a) Tabulated list of adverse reactions

System organ class	Frequent	Less frequent
Infections and infestations		Post-operative wound infections
Blood and the lymphatic system disorders	Anaemia, bleeding (various sites including rare cases of intracranial/ intracerebral and retroperitoneal bleedings), purpura	Thrombocytopenia, thrombocythaemia, abnormal platelets, coagulation disorder
Immune system disorders		Allergic reactions (including very rare reports of angioedema, anaphylactoid/anaphylactic reaction)
Metabolism and		Hypokalaemia

nutrition disorders		
Psychiatric disorders	Insomnia	
Nervous system disorders		Headache; anxiety, confusion, dizziness, somnolence, vertigo
Vascular disorders		Hypotension
Respiratory, thoracic and mediastinal disorders		Dyspnoea, coughing
Gastrointestinal disorders		Nausea, vomiting, abdominal pain, dyspepsia, gastritis, constipation, diarrhoea
Hepato-biliary disorders		Abnormal liver function tests, increased hepatic enzymes, hyperbilirubinaemia
Skin and subcutaneous tissue disorders		Rash, pruritus, localized bullous eruption, wound secretion
Renal and urinary disorders	Urinary tract infections	Urinary retention
General disorders and administrative site conditions	Oedema, peripheral oedema	Fever. reaction at injection site, chest pain, leg pain, fatigue, flushing, syncope

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to:

SAHPRA: https://www.sahpra.org.za/health-products-vigilance/

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088

4.9. Overdose

Symptoms

ARIXTRA 2,5 mg/0,5 ml doses above the recommended regimen, may lead to an increased risk of bleeding.

Treatment

There is no antidote for ARIXTRA 2,5 mg/0,5 ml . Overdosage associated with bleeding complications should lead to treatment discontinuation, search for the primary cause and initiation of appropriate therapy, which may include surgical haemostasis, blood replacements, fresh plasma transfusion, plasmapheresis should be considered

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Category and class: A 8.2 Anticoagulants

Pharmacotherapeutic group: Antithrombotic agents

ATC code: B01AX05

Mechanism of action

Fondaparinux is a synthetic and specific 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 neutralisation of factor Xa by antithrombin. Neutralisation of factor Xa interrupts the blood coagulation cascade and inhibits both thrombin formation and thrombus development. Fondaparinux does not inactivate thrombin (activated factor II) and at therapeutic doses has no

significant effect on platelets. At the recommended dose, it does not affect fibrinolytic activity or bleeding time.

Spontaneous reports of elevated aPTT (activated partial thromboplastin time) have been received at the 2,5 mg dose.

5.2 Pharmacokinetic properties

Absorption:

After subcutaneous dosing, fondaparinux is completely and rapidly absorbed, the absolute bioavailability being 100 %. Following a single subcutaneous injection of 2,5 mg of fondaparinux, peak plasma concentration (C_{max} = 0,34 mg/L) is obtained 2 hours post-dosing. Plasma concentrations of half the mean C_{max} values are reached 25 minutes post-dosing.

Mean (SD) pharmacokinetic parameters of fondaparinux following a single subcutaneous injection of fondaparinux 2,5 mg in young healthy subjects are provided below.

T_{max} (h)	C_{max} (mg/L)	$AUC_{0\text{-}inf}$ (mg.h/L)	$T_{1/2}$ (h)	Plasma clearance (ml /min)	Distribution volume (L)
1,7 (0,4)	0,34 (0,04)	6,65 (1,20)	17,2 (3,2)	5,6 (0,9)	8,2 (1,1)

Pharmacokinetics of fondaparinux are linear in the range of 2 to 8 mg by subcutaneous route. At steady state, mean plasma concentration 2 hours post-dosing ranged between 0,32 and 0,47 mg/L in patients undergoing orthopaedic surgeries receiving fondaparinux 2,5 mg.

Distribution:

The distribution volume of fondaparinux is limited (7 to 11 L) and is consistent with blood volume. Fondaparinux is highly (at least 97,0 %) and specifically bound to ATIII protein and does not bind significantly to other plasma proteins, including platelet factor 4 (PF4).

Biotransformation

Has not been investigated.

Elimination

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

Special populations

Paediatric patients

Fondaparinux has not been investigated in this population.

Elderly patients

In patients over 75 years, the estimated plasma clearance was 1,2 to 1,4 times lower than in patients less than 65 years.

Renally impaired patients

Fondaparinux elimination is prolonged in patients with renal impairment since the major route of elimination is urinary excretion of unchanged fondaparinux.

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 hours in moderate and 72 hours in patients with severe renal impairment.

Hepatic impairment

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 fondaparinux has not been studied in patients with severe hepatic impairment (see section 4.2 and 4.4).

Body weight

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

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Hydrochloric acid (for pH adjustment), sodium chloride, sodium hydroxide (for pH adjustment), water for injection.

6.2 Incompatibilities:

In the absence of compatibility studies, ARIXTRA 2,5 mg/0,5 ml must not be mixed with other medicines.

6.3 Shelf life

36 months

6.4. Special precautions for storage

Store at or below 25 °C.

Do not freeze.

Keep in original packaging until required for use.

6.5. Nature and contents of container

Pre-filled, single use, clear and colourless glass syringe with a blue plunger affixed with a 27 gauge (0,4 mm) x 12,7 mm needle and an automatic safety system. 2, 7, 10 and 20 syringes are packed in an outer cardboard carton.

Not all pack sizes are necessarily marketed.

The needle protection system of the ARIXTRA 2,5 mg/0,5 ml pre-filled syringe has been designed to protect healthcare providers from needle stick injuries following injection.

6.6. Special precautions for disposal and other handling

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

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 50 ml) 0,9 % sodium chloride mini-bag (see section 4.2).

Parenteral medicines should be inspected visually for visible particles and discolouration prior to administration (see section 4.2).

7. HOLDER OF CERTIFICATE OF REGISTRATION:

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

8.REGISTRATION NUMBER

36/8.2/0364

9. DATE OF FIRST AUTHORISATION

23 July 2004

10. DATE OF REVISION OF TEXT

19 April 2022

Die Afrikaanse Professionele Inligting is op versoek beskikbaar. Mediese Blitslyn: 0800 118 088.

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