HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ARIXTRA safely and effectively. See full prescribing information for ARIXTRA.

ARIXTRA (fondaparinux sodium) Solution for subcutaneous injection
Initial U.S. Approval: 2001

WARNING: SPINAL/EPIDURAL HEMATOMAS

Epidural or spinal hematomas may occur in patients who are anticoagulated with low molecular weight heparins (LMWH), heparinoids, or fondaparinux sodium and are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- **use of indwelling epidural catheters**
- **concomitant use of other drugs that affect hemostasis, such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, or other anticoagulants**
- **a history of traumatic or repeated epidural or spinal puncture**
- **a history of spinal deformity or spinal surgery**

Monitor patients frequently for signs and symptoms of neurologic impairment. If neurologic compromise is noted, urgent treatment is necessary.

Consider the benefit and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis. *[See Warnings and Precautions (5.5) and Drug Interactions (7).]*

----------RECENT MAJOR CHANGES----------

Contraindications (4) 09/2013

----------INDICATIONS AND USAGE----------

ARIXTRA is a Factor Xa inhibitor (anticoagulant) indicated for:

- Prophylaxis of deep vein thrombosis (DVT) in patients undergoing hip fracture surgery (including extended prophylaxis), hip replacement surgery, knee replacement surgery, or abdominal surgery. (1.1)
- Treatment of DVT or acute pulmonary embolism (PE) when administered in conjunction with warfarin. (1.2, 1.3)

---------- DOSAGE AND ADMINISTRATION ----------

- Prophylaxis of deep vein thrombosis: ARIXTRA 2.5 mg subcutaneously once daily after hemostasis has been established. The initial dose should be given no earlier than 6 to 8 hours after surgery and continued for 5 to 9 days. For patients undergoing hip fracture surgery, extended prophylaxis up to 24 additional days is recommended. (2.1, 2.2)
- Treatment of deep vein thrombosis and pulmonary embolism: ARIXTRA 5 mg (body weight <50 kg), 7.5 mg (50 to 100 kg), or 10 mg (>100 kg) subcutaneously once daily. Treatment should continue for at least 5 days until INR 2 to 3 achieved with warfarin sodium. (2.3)

Do not use as intramuscular injection. For subcutaneous use, do not mix with other injections or infusions.

---------- DOSAGE FORMS AND STRENGTHS ----------

Single-dose, prefilled syringes containing 2.5 mg, 5 mg, 7.5 mg, or 10 mg of fondaparinux. (3)

----------CONTRAINDICATIONS----------

ARIXTRA is contraindicated in the following conditions: (4)

- Severe renal impairment (creatinine clearance <30 mL/min) in prophylaxis or treatment of venous thromboembolism.
- Active major bleeding.
- Bacterial endocarditis.
- Thrombocytopenia associated with a positive *in vitro* test for anti-platelet antibody in the presence of fondaparinux sodium.
- Body weight <50 kg (venous thromboembolism prophylaxis only).
- History of serious hypersensitivity reaction (e.g., angioedema, anaphylactoid/anaphylactic reactions) to ARIXTRA.

---------- WARNINGS AND PRECAUTIONS ----------

- Use with caution in patients who have conditions or are taking concomitant medications that increase risk of hemorrhage. (5.1)
- Bleeding risk is increased in renal impairment and in patients with low body weight <50 kg. (5.2, 5.3)
- Thrombocytopenia can occur with administration of ARIXTRA. (5.4)
- Periodic routine complete blood counts (including platelet counts), serum creatinine level, and stool occult blood tests are recommended (5.6)
- The packaging (needle guard) contains dry natural rubber and may cause allergic reactions in latex sensitive individuals (5.7)

---------- ADVERSE REACTIONS ----------

The most common adverse reactions associated with the use of ARIXTRA are bleeding complications. (6.1) Mild local irritation (injection site bleeding, rash, and pruritus) may occur following subcutaneous injection. (6.2)
Anemia, insomnia, increased wound drainage, hypokalemia, dizziness, hypotension, confusion, bullous eruption, hematoma, post-operative hemorrhage, and purpura may occur. (6.4)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

Discontinue agents that may enhance the risk of hemorrhage prior to initiation of therapy with ARIXTRA unless essential. If co-administration is necessary, monitor patients closely for hemorrhage. (7)

---------- USE IN SPECIFIC POPULATIONS ----------

- Safety and effectiveness of ARIXTRA in pediatric patients have not been established. Because the risk for bleeding during treatment with ARIXTRA is increased in adults who weigh <50 kg, bleeding may be a particular safety concern for use of ARIXTRA in the pediatric population. (4, 5.3)
- Because elderly patients are more likely to have reduced renal function, ARIXTRA should be used with caution in these patients. (8.5)
- The risk of bleeding is increased with reduced renal or hepatic function. (8.6, 8.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 09/2013

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: SPINAL/EPIDURAL HEMATOMAS

Epidural or spinal hematomas may occur in patients who are anticoagulated with low molecular weight heparins (LMWH), heparinoids, or fondaparinux sodium and are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- use of indwelling epidural catheters
- concomitant use of other drugs that affect hemostasis, such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, or other anticoagulants
- a history of traumatic or repeated epidural or spinal puncture
- a history of spinal deformity or spinal surgery

Monitor patients frequently for signs and symptoms of neurologic impairment. If neurologic compromise is noted, urgent treatment is necessary.

Consider the benefit and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis. *[See Warnings and Precautions (5.5) and Drug Interactions (7).]*

1 INDICATIONS AND USAGE

1.1 Prophylaxis of Deep Vein Thrombosis

ARIXTRA® is indicated for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE):

- in patients undergoing hip fracture surgery, including extended prophylaxis;
- in patients undergoing hip replacement surgery;
- in patients undergoing knee replacement surgery;
- in patients undergoing abdominal surgery who are at risk for thromboembolic complications.

1.2 Treatment of Acute Deep Vein Thrombosis

ARIXTRA is indicated for the treatment of acute deep vein thrombosis when administered in conjunction with warfarin sodium.

1.3 Treatment of Acute Pulmonary Embolism

ARIXTRA is indicated for the treatment of acute pulmonary embolism when administered in conjunction with warfarin sodium when initial therapy is administered in the hospital.

2 DOSAGE AND ADMINISTRATION

Do not mix other medications or solutions with ARIXTRA. Administer ARIXTRA only subcutaneously.

2.1 Deep Vein Thrombosis Prophylaxis Following Hip Fracture, Hip Replacement, and Knee Replacement Surgery

In patients undergoing hip fracture, hip replacement, or knee replacement surgery, the recommended dose of ARIXTRA is 2.5 mg administered by subcutaneous injection once daily after hemostasis has been established. Administer the initial dose no earlier than 6 to 8 hours after surgery. Administration of ARIXTRA earlier than 6 hours after surgery increases the risk of major bleeding. The usual duration of therapy is 5 to 9 days; up to 11 days of therapy was administered in clinical trials.

In patients undergoing hip fracture surgery, an extended prophylaxis course of up to 24 additional days is recommended. In patients undergoing hip fracture surgery, a total of 32 days (peri-operative and extended prophylaxis) was administered in clinical trials. *[See Warnings and Precautions (5.6), Adverse Reactions (6), and Clinical Studies (14).]*

2.2 Deep Vein Thrombosis Prophylaxis Following Abdominal Surgery

In patients undergoing abdominal surgery, the recommended dose of ARIXTRA is 2.5 mg administered by subcutaneous injection once daily after hemostasis has been established. Administer the initial dose no earlier than 6 to 8 hours after surgery. Administration of ARIXTRA earlier than 6 hours after surgery increases the risk of major bleeding. The usual duration of administration is 5 to 9 days, and up to 10 days of ARIXTRA was administered in clinical trials.

2.3 Deep Vein Thrombosis and Pulmonary Embolism Treatment

In patients with acute symptomatic DVT and in patients with acute symptomatic PE, the recommended dose of ARIXTRA is 5 mg (body weight <50 kg), 7.5 mg (body weight 50 to 100 kg), or 10 mg (body weight >100 kg) by subcutaneous injection once daily (ARIXTRA treatment regimen). Initiate concomitant treatment with warfarin sodium as soon as possible, usually within 72 hours. Continue treatment with ARIXTRA for at least 5 days and until a therapeutic oral anticoagulant effect is established (INR 2 to 3). The usual duration of administration of ARIXTRA is 5 to 9 days; up to 26 days of ARIXTRA injection was administered in clinical trials. *[See Warnings and Precautions (5.6), Adverse Reactions (6), and Clinical Studies (14).]*

2.4 Hepatic Impairment

No dose adjustment is recommended in patients with mild to moderate hepatic impairment, based upon single-dose pharmacokinetic data. Pharmacokinetic data are not available for patients with severe hepatic impairment. Patients with hepatic impairment may be particularly vulnerable to bleeding during ARIXTRA therapy. Observe these patients closely for signs and symptoms of bleeding. *[See Clinical Pharmacology (12.4).]*

2.5 Instructions for Use

ARIXTRA Injection is provided in a single-dose, prefilled syringe affixed with an automatic needle protection system. ARIXTRA is administered by subcutaneous injection. It must not be administered by intramuscular 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 the patients are trained in subcutaneous injection techniques.

Prior to administration, visually inspect ARIXTRA to ensure the solution is clear and free of particulate matter.

To avoid the loss of drug when using the prefilled syringe, do not expel the air bubble from the syringe before the injection. Administration should be made in the fatty tissue, alternating injection sites (e.g., between the left and right anterolateral or the left and right posterolateral abdominal wall).

To administer ARIXTRA:

1. Wipe the surface of the injection site with an alcohol swab.
2. Hold the syringe with either hand and use your other hand to twist the rigid needle guard (covers the needle) counter-clockwise. Pull the rigid needle guard straight off the needle (Figure 1). Discard the needle guard.
3. Do not try to remove the air bubbles from the syringe before giving the injection.
4. Pinch a fold of skin at the injection site between your thumb and forefinger and hold it throughout the injection.
5. Hold the syringe with your thumb on the top pad of the plunger rod and your next 2 fingers on the finger grips on the syringe barrel. Pay attention to avoid sticking yourself with the exposed needle (Figure 2).

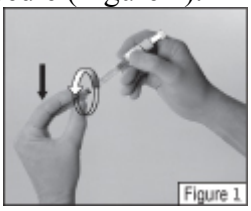


Figure 1

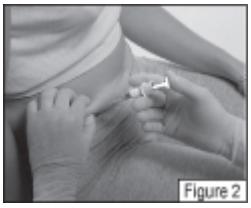


Figure 2

6. Insert the full length of the syringe needle perpendicularly into the skin fold held between the thumb and forefinger (Figure 3).
7. Push the plunger rod firmly with your thumb as far as it will go. This will ensure you have injected all the contents of the syringe (Figure 4).

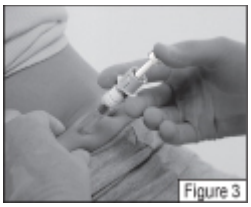


Figure 3

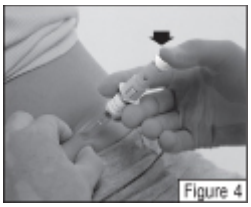


Figure 4

8. When you have injected all the contents of the syringe, the plunger should be released. The plunger will then rise automatically while the needle withdraws from the skin and retracts into the security sleeve. Discard the syringe into the sharps container.
9. You will know that the syringe has worked when:

- The needle is pulled back into the security sleeve and the white safety indicator appears above the upper body.
- You may also hear or feel a soft click when the plunger rod is released fully.

3 DOSAGE FORMS AND STRENGTHS

Single-dose, prefilled syringes containing either 2.5 mg, 5 mg, 7.5 mg, or 10 mg of fondaparinux.

4 CONTRAINDICATIONS

ARIXTRA is contraindicated in the following conditions:

- Severe renal impairment (creatinine clearance [CrCl] <30 mL/min). *[See Warnings and Precautions (5.2) and Use in Specific Populations (8.6).]*
- Active major bleeding.
- Bacterial endocarditis.
- Thrombocytopenia associated with a positive *in vitro* test for anti-platelet antibody in the presence of fondaparinux sodium.
- Body weight <50 kg (venous thromboembolism [VTE] prophylaxis only) *[see Warnings and Precautions (5.3)]*.
- History of serious hypersensitivity reaction (e.g., angioedema, anaphylactoid/anaphylactic reactions) to ARIXTRA.

5 WARNINGS AND PRECAUTIONS

5.1 Hemorrhage

Use ARIXTRA with extreme caution in conditions with increased risk of hemorrhage, such as congenital or acquired bleeding disorders, active ulcerative and angiodysplastic gastrointestinal disease, hemorrhagic stroke, uncontrolled arterial hypertension, diabetic retinopathy, or shortly after brain, spinal, or ophthalmological surgery. Isolated cases of elevated aPTT temporally associated with bleeding events have been reported following administration of ARIXTRA (with or without concomitant administration of other anticoagulants) *[see Adverse Reactions (6.5)]*.

Do not administer agents that enhance the risk of hemorrhage with ARIXTRA unless essential for the management of the underlying condition, such as vitamin K antagonists for the treatment of VTE. If co-administration is essential, closely monitor patients for signs and symptoms of bleeding.

Do not administer the initial dose of ARIXTRA earlier than 6 to 8 hours after surgery. Administration earlier than 6 hours after surgery increases risk of major bleeding *[see Dosage and Administration (2) and Adverse Reactions (6.1)]*.

5.2 Renal Impairment and Bleeding Risk

ARIXTRA increases the risk of bleeding in patients with impaired renal function due to reduced clearance *[see Clinical Pharmacology (12.4)]*.

The incidence of major bleeding by renal function status reported in clinical trials of patients receiving ARIXTRA for VTE surgical prophylaxis is provided in Table 1. In these patient populations, the following is recommended:

- Do not use ARIXTRA for VTE prophylaxis and treatment in patients with CrCl <30 mL/min *[see Contraindications (4)]*.
- Use ARIXTRA with caution in patients with CrCl 30 to 50 mL/min.

Table 1. Incidence of Major Bleeding in Patients Treated With ARIXTRA by Renal Function Status for Surgical Prophylaxis and Treatment of Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE)

		Degree of Renal Impairment			
Population	**Timing of Dose**	**Normal % (n/N)**	**Mild % (n/N)**	**Moderate % (n/N)**	**Severe % (n/N)**
CrCl (mL/min)		**≥80**	**≥50 - <80**	**≥30 - <50**	**<30**
Orthopedic surgery[a]	Overall	1.6% (25/1,565)	2.4% (31/1,288)	3.8% (19/504)	4.8% (4/83)
	6-8 hours after surgery	1.8% (16/905)	2.2% (15/675)	2.3% (6/265)	0% (0/40)
Abdominal surgery	Overall	2.1% (13/606)	3.6% (22/613)	6.7% (12/179)	7.1% (1/14)
	6-8 hours after surgery	2.1% (10/467)	3.3% (16/481)	5.8% (8/137)	7.7% (1/13)
DVT and PE Treatment		0.4% (4/1,132)	1.6% (12/733)	2.2% (7/318)	7.3% (4/55)

CrCl = creatinine clearance.

[a] Hip fracture, hip replacement, and knee replacement surgery prophylaxis.

Assess renal function periodically in patients receiving ARIXTRA. Discontinue the drug immediately in patients who develop severe renal impairment while on therapy. After discontinuation of ARIXTRA, 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 may persist even longer in patients with renal impairment *[see Clinical Pharmacology (12.4)]*.

5.3 Body Weight <50 Kg and Bleeding Risk

ARIXTRA increases the risk for bleeding in patients who weigh less than 50 kg, compared to patients with higher weights.

In patients who weigh less than 50 kg:

- Do not administer ARIXTRA as prophylactic therapy for patients undergoing hip fracture, hip replacement, or knee replacement surgery and abdominal surgery *[see Contraindications (4)]*.
- Use ARIXTRA with caution in the treatment of PE and DVT.

During the randomized clinical trials of VTE prophylaxis in the peri-operative period following hip fracture, hip replacement, or knee replacement surgery and abdominal surgery, major bleeding occurred at a higher rate among patients with a body weight <50 kg compared to those with a body weight >50 kg (5.4% versus 2.1% in patients undergoing hip fracture, hip replacement, or knee replacement surgery; 5.3% versus 3.3% in patients undergoing abdominal surgery).

5.4 Thrombocytopenia

Thrombocytopenia can occur with the administration of ARIXTRA. Thrombocytopenia of any degree should be monitored closely. Discontinue ARIXTRA if the platelet count falls below 100,000/mm^3. Moderate thrombocytopenia (platelet counts between 100,000/mm^3 and 50,000/mm^3) occurred at a rate of 3.0% in patients given ARIXTRA 2.5 mg in the peri-operative hip fracture, hip replacement, or knee replacement surgery and abdominal surgery 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 in these clinical trials. During extended prophylaxis, no cases of moderate or severe thrombocytopenia were reported.

Moderate thrombocytopenia occurred at a rate of 0.5% in patients given the ARIXTRA treatment regimen in the DVT and PE treatment clinical trials. Severe thrombocytopenia occurred at a rate of 0.04% in patients given the ARIXTRA treatment regimen in the DVT and PE treatment clinical trials.

Isolated occurrences of thrombocytopenia with thrombosis that manifested similar to heparin-induced thrombocytopenia have been reported with the use of ARIXTRA in postmarketing experience. *[See Adverse Reactions (6.5).]*

5.5 Neuraxial Anesthesia and Post-operative Indwelling Epidural Catheter Use

Spinal or epidural hematomas, which may result in long-term or permanent paralysis, can occur with the use of anticoagulants and neuraxial (spinal/epidural) anesthesia or spinal puncture. The risk of these events may be higher with post-operative use of indwelling epidural catheters or concomitant use of other drugs affecting hemostasis such as NSAIDs *[see Boxed Warning]*. In the postmarketing experience, epidural or spinal hematoma has been reported in association with the use of ARIXTRA by subcutaneous (SC) injection. Monitor patients undergoing these procedures for signs and symptoms of neurologic impairment. Consider the potential risks and benefits before neuraxial intervention in patients anticoagulated or who may be anticoagulated for thromboprophylaxis.

5.6 Monitoring: Laboratory Tests

Routine coagulation tests such as Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT) are relatively insensitive measures of the activity of ARIXTRA

and international standards of heparin or LMWH are not calibrators to measure anti-Factor Xa activity of ARIXTRA. If unexpected changes in coagulation parameters or major bleeding occur during therapy with ARIXTRA, discontinue ARIXTRA. In postmarketing experience, isolated occurrences of aPTT elevations have been reported following administration of ARIXTRA *[see Adverse Reactions (6.5)]*.

Periodic routine complete blood counts (including platelet count), serum creatinine level, and stool occult blood tests are recommended during the course of treatment with ARIXTRA.

The anti-Factor Xa activity of fondaparinux sodium can be measured by anti-Xa assay using the appropriate calibrator (fondaparinux). The activity of fondaparinux sodium is expressed in milligrams (mg) of the fondaparinux and cannot be compared with activities of heparin or low molecular weight heparins. *[See Clinical Pharmacology (12.2, 12.3).]*

5.7 Latex

The packaging (needle guard) of the prefilled syringe of ARIXTRA contains dry natural latex rubber that may cause allergic reactions in latex sensitive individuals.

6 ADVERSE REACTIONS

The most serious adverse reactions reported with ARIXTRA are bleeding complications and thrombocytopenia *[see Warnings and Precautions (5)]*.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The adverse reaction information below is based on data from 8,877 patients exposed to ARIXTRA in controlled trials of hip fracture, hip replacement, major knee, or abdominal surgeries, and DVT and PE treatment. These trials consisted of the following:

- 2 peri-operative dose-response trials (n = 989)
- 4 active-controlled peri-operative VTE prophylaxis trials with enoxaparin sodium (n = 3,616), an extended VTE prophylaxis trial (n = 327), and an active-controlled trial with dalteparin sodium (n = 1,425)
- a dose-response trial (n = 111) and an active-controlled trial with enoxaparin sodium in DVT treatment (n = 1,091)
- an active-controlled trial with heparin in PE treatment (n = 1,092)

6.1 Hemorrhage

During administration of ARIXTRA, the most common adverse reactions were bleeding complications *[see Warnings and Precautions (5.1)]*.

Hip Fracture, Hip Replacement, and Knee Replacement Surgery: The rates of major bleeding events reported during the hip fracture, hip replacement, or knee replacement surgery clinical trials with ARIXTRA 2.5 mg are provided in Table 2.

Table 2. Bleeding Across Randomized, Controlled Hip Fracture, Hip Replacement, and Knee Replacement Surgery Studies

	Peri-Operative Prophylaxis (Day 1 to Day 7 ± 1 post-surgery)		Extended Prophylaxis (Day 8 to Day 28 ± 2 post-surgery)	
	ARIXTRA 2.5 mg SC once daily N = 3,616	**Enoxaparin Sodium[a, b]** N = 3,956	**ARIXTRA 2.5 mg SC once daily** N = 327	**Placebo SC once daily** N = 329
Major bleeding[c]	96 (2.7%)	75 (1.9%)	8 (2.4%)	2 (0.6%)
Hip fracture	18/831 (2.2%)	19/842 (2.3%)	8/327 (2.4%)	2/329 (0.6%)
Hip replacement	67/2,268 (3.0%)	55/2,597 (2.1%)	—	—
Knee replacement	11/517 (2.1%)	1/517 (0.2%)	—	—
Fatal bleeding	0 (0.0%)	1 (<0.1%)	0 (0.0%)	0 (0.0%)
Non-fatal bleeding at critical site	0 (0.0%)	1 (<0.1%)	0 (0.0%)	0 (0.0%)
Re-operation due to bleeding	12 (0.3%)	10 (0.3%)	2 (0.6%)	2 (0.6%)
BI ≥2[d]	84 (2.3%)	63 (1.6%)	6 (1.8%)	0 (0.0%)
Minor bleeding[e]	109 (3.0%)	116 (2.9%)	5 (1.5%)	2 (0.6%)

[a] Enoxaparin sodium dosing regimen: 30 mg every 12 hours or 40 mg once daily.

[b] Not approved for use in patients undergoing hip fracture surgery.

[c] Major bleeding was defined as clinically overt bleeding that was (1) fatal, (2) bleeding at critical site (e.g. intracranial, retroperitoneal, intraocular, pericardial, spinal, or into adrenal gland), (3) associated with re-operation at operative site, or (4) with a bleeding index (BI) ≥2.

[d] BI ≥2: Overt bleeding associated only with a bleeding index (BI) ≥2 calculated as [number of whole blood or packed red blood cell units transfused + [(pre-bleeding) – (post-bleeding)] hemoglobin (g/dL) values].

[e] Minor bleeding was defined as clinically overt bleeding that was not major.

A separate analysis of major bleeding across all randomized, controlled, peri-operative, prophylaxis clinical studies of hip fracture, hip replacement, or knee replacement surgery according to the time of the first injection of ARIXTRA after surgical closure was performed in patients who received ARIXTRA only post-operatively. In this analysis, the incidences of major bleeding were as follows: <4 hours was 4.8% (5/104), 4 to 6 hours was 2.3% (28/1,196), 6 to 8 hours was 1.9% (38/1,965). In all studies, the majority (≥75%) of the major bleeding events occurred during the first 4 days after surgery.

Abdominal Surgery: In a randomized study of patients undergoing abdominal surgery, ARIXTRA 2.5 mg once daily (n = 1,433) was compared with dalteparin 5,000 IU once daily (n = 1,425). Bleeding rates are shown in Table 3.

Table 3. Bleeding in the Abdominal Surgery Study

	ARIXTRA 2.5 mg SC once daily	**Dalteparin Sodium 5,000 IU SC once daily**
	N = 1,433	N = 1,425
Major bleeding[a]	49 (3.4%)	34 (2.4%)
Fatal bleeding	2 (0.1%)	2 (0.1%)
Non-fatal bleeding at critical site	0 (0.0%)	0 (0.0%)
Other non-fatal major bleeding		
Surgical site	38 (2.7%)	26 (1.8%)
Non-surgical site	9 (0.6%)	6 (0.4%)
Minor bleeding[b]	31 (2.2%)	23 (1.6%)

[a] Major bleeding was defined as bleeding that was (1) fatal, (2) bleeding at the surgical site leading to intervention, (3) non-surgical bleeding at a critical site (e.g. intracranial, retroperitoneal, intraocular, pericardial, spinal, or into adrenal gland), or leading to an intervention, and/or with a bleeding index (BI) ≥2.

[b] Minor bleeding was defined as clinically overt bleeding that was not major.

The rates of major bleeding according to the time interval following the first ARIXTRA injection were as follows: <6 hours was 3.4% (9/263) and 6 to 8 hours was 2.9% (32/1112).

Treatment of Deep Vein Thrombosis and Pulmonary Embolism: The rates of bleeding events reported during the DVT and PE clinical trials with the ARIXTRA injection treatment regimen are provided in Table 4.

Table 4. Bleeding[a] in Deep Vein Thrombosis and Pulmonary Embolism Treatment Studies

	ARIXTRA N = 2,294	**Enoxaparin Sodium** N = 1,101	**Heparin aPTT adjusted IV** N = 1,092
Major bleeding[b]	28 (1.2%)	13 (1.2%)	12 (1.1%)
Fatal bleeding	3 (0.1%)	0 (0.0%)	1 (0.1%)
Non-fatal bleeding at a critical site	3 (0.1%)	0 (0.0%)	2 (0.2%)
Intracranial bleeding	3 (0.1%)	0 (0.0%)	1 (0.1%)
Retro-peritoneal bleeding	0 (0.0%)	0 (0.0%)	1 (0.1%)
Other clinically overt bleeding[c]	22 (1.0%)	13 (1.2%)	10 (0.9%)
Minor bleeding[d]	70 (3.1%)	33 (3.0%)	57 (5.2%)

[a] Bleeding rates are during the study drug treatment period (approximately 7 days). Patients were also treated with vitamin K antagonists initiated within 72 hours after the first study drug administration.

[b] Major bleeding was defined as clinically overt: –and/or contributing to death – and/or in a critical organ including intracranial, retroperitoneal, intraocular, spinal, pericardial, or adrenal gland – and/or associated with a fall in hemoglobin level ≥2 g/dL – and/or leading to a transfusion ≥2 units of packed red blood cells or whole blood.

[c] Clinically overt bleeding with a 2 g/dL fall in hemoglobin and/or leading to transfusion of PRBC or whole blood ≥2 units.

[d] Minor bleeding was defined as clinically overt bleeding that was not major.

6.2 Local Reactions

Local irritation (injection site bleeding, rash, and pruritus) may occur following subcutaneous injection of ARIXTRA.

6.3 Elevations of Serum Aminotransferases

In the peri-operative prophylaxis randomized clinical trials of 7 ± 2 days, asymptomatic increases in aspartate (AST) and alanine (ALT) aminotransferase levels greater than 3 times the upper limit of normal were reported in 1.7% and 2.6% of patients, respectively, during treatment with ARIXTRA 2.5 mg once daily versus 3.2% and 3.9% of patients, respectively, during treatment with enoxaparin sodium 30 mg every 12 hours or 40 mg once daily enoxaparin sodium. These elevations are reversible and rarely associated with increases in bilirubin. In the extended prophylaxis clinical trial, no significant differences in AST and ALT levels between ARIXTRA 2.5 mg and placebo-treated patients were observed.

In the DVT and PE treatment clinical trials, asymptomatic increases in AST and ALT levels greater than 3 times the upper limit of normal of the laboratory reference range were reported in 0.7% and 1.3% of patients, respectively, during treatment with ARIXTRA. In

comparison, these increases were reported in 4.8% and 12.3% of patients, respectively, in the DVT treatment trial during treatment with enoxaparin sodium 1 mg/kg every 12 hours and in 2.9% and 8.7% of patients, respectively, in the PE treatment trial during treatment with aPTT adjusted heparin.

Since aminotransferase determinations are important in the differential diagnosis of myocardial infarction, liver disease, and pulmonary emboli, elevations that might be caused by drugs like ARIXTRA should be interpreted with caution.

6.4 Other Adverse Reactions

Other adverse reactions that occurred during treatment with ARIXTRA in clinical trials with patients undergoing hip fracture, hip replacement, or knee replacement surgery are provided in Table 5.

Table 5. Adverse Reactions Across Randomized, Controlled, Hip Fracture Surgery, Hip Replacement Surgery, and Knee Replacement Surgery Studies

	Peri-Operative Prophylaxis (Day 1 to Day 7 ± 1 post-surgery)		**Extended Prophylaxis (Day 8 to Day 28 ± 2 post-surgery)**	
Adverse Reactions	**ARIXTRA 2.5 mg SC once daily**	**Enoxaparin Sodium[a, b]**	**ARIXTRA 2.5 mg SC once daily**	**Placebo SC once daily**
	N = 3,616	N = 3,956	N = 327	N = 329
Anemia	707 (19.6%)	670 (16.9%)	5 (1.5%)	4 (1.2%)
Insomnia	179 (5.0%)	214 (5.4%)	3 (0.9%)	1 (0.3%)
Wound drainage increased	161 (4.5%)	184 (4.7%)	2 (0.6%)	0 (0.0%)
Hypokalemia	152 (4.2%)	164 (4.1%)	0 (0.0%)	0 (0.0%)
Dizziness	131 (3.6%)	165 (4.2%)	2 (0.6%)	0 (0.0%)
Purpura	128 (3.5%)	137 (3.5%)	0 (0.0%)	0 (0.0%)
Hypotension	126 (3.5%)	125 (3.2%)	1 (0.3%)	0 (0.0%)
Confusion	113 (3.1%)	132 (3.3%)	4 (1.2%)	1 (0.3%)
Bullous eruption[c]	112 (3.1%)	102 (2.6%)	0 (0.0%)	1 (0.3%)
Hematoma	103 (2.8%)	109 (2.8%)	7 (2.1%)	1 (0.3%)
Post-operative hemorrhage	85 (2.4%)	69 (1.7%)	2 (0.6%)	2 (0.6%)

[a] Enoxaparin sodium dosing regimen: 30 mg every 12 hours or 40 mg once daily.

[b] Not approved for use in patients undergoing hip fracture surgery.

[c] Localized blister coded as bullous eruption.

Adverse reactions in the abdominal surgery study and in the VTE treatment trials generally occurred at lower rates than in the hip and knee surgery trials described above. The most common adverse reaction in the abdominal surgery trial was post-operative wound infection (4.9%), and the most common adverse reaction in the VTE treatment trials was epistaxis (1.3%).

6.5 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of ARIXTRA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Isolated occurrences of thrombocytopenia with thrombosis that manifested similar to heparin-induced thrombocytopenia have been reported in the postmarketing experience and isolated cases of elevated aPTT temporally associated with bleeding events have been reported following administration of ARIXTRA (with or without concomitant administration of other anticoagulants) *[see Warnings and Precautions (5.4)]*.

Serious allergic reactions, including angioedema, anaphylactoid/anaphylactic reactions have been reported with the use of ARIXTRA *[see Contraindications (4)]*.

7 DRUG INTERACTIONS

In clinical studies performed with ARIXTRA, the concomitant use of oral anticoagulants (warfarin), platelet inhibitors (acetylsalicylic acid), NSAIDs (piroxicam), and digoxin did not significantly affect the pharmacokinetics/pharmacodynamics of fondaparinux sodium. In addition, ARIXTRA neither influenced the pharmacodynamics of warfarin, acetylsalicylic acid, piroxicam, and digoxin, nor the pharmacokinetics of digoxin at steady state.

Agents that may enhance the risk of hemorrhage should be discontinued prior to initiation of therapy with ARIXTRA unless these agents are essential. If co-administration is necessary, monitor patients closely for hemorrhage. *[See Warnings and Precautions (5.1).]*

In an *in vitro* study in human liver microsomes, inhibition of CYP2A6 hydroxylation of coumarin by fondaparinux (200 micromolar i.e., 350 mg/L) was 17 to 28%. Inhibition of the other isozymes evaluated (CYPs 1A2, 2C9, 2C19, 2D6, 3A4, and 3E1) was 0 to 16%. Since fondaparinux does not markedly inhibit CYP450s (CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4) *in vitro*, fondaparinux sodium is not expected to significantly interact with other drugs *in vivo* by inhibition of metabolism mediated by these isozymes.

Since fondaparinux sodium does not bind significantly to plasma proteins other than ATIII, no drug interactions by protein-binding displacement are expected.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B. Reproduction studies have been performed in pregnant rats at subcutaneous doses up to 10 mg/kg/day (about 32 times the recommended human dose based on body surface area) and pregnant rabbits at subcutaneous doses up to 10 mg/kg/day (about 65 times the recommended human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to fondaparinux sodium. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, ARIXTRA should be used during pregnancy only if clearly needed.

8.3 Nursing Mothers

Fondaparinux sodium was found to be excreted in the milk of lactating rats. However, it is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ARIXTRA is administered to a nursing mother.

8.4 Pediatric Use

Safety and effectiveness of ARIXTRA in pediatric patients have not been established. Because risk for bleeding during treatment with ARIXTRA is increased in adults who weigh <50 kg, bleeding may be a particular safety concern for use of ARIXTRA in the pediatric population *[see Warnings and Precautions (5.3)]*.

8.5 Geriatric Use

In clinical trials the efficacy of ARIXTRA in the elderly (65 years or older) was similar to that seen in patients younger than 65 years; however, serious adverse events increased with age. Exercise caution when using ARIXTRA in elderly patients, paying particular attention to dosing directions and concomitant medications (especially anti-platelet medication). *[See Warnings and Precautions (5.1).]*

Fondaparinux sodium is substantially excreted by the kidney, and the risk of adverse reactions to ARIXTRA may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, assess renal function prior to ARIXTRA administration. *[See Contraindications (4), Warnings and Precautions (5.2), and Clinical Pharmacology (12.4).]*

In the peri-operative hip fracture, hip replacement, or knee replacement surgery clinical trials with patients receiving ARIXTRA 2.5 mg, serious adverse events increased with age for patients receiving ARIXTRA. The incidence of major bleeding in clinical trials of ARIXTRA by age is provided in Table 6.

Table 6. Incidence of Major Bleeding in Patients Treated With ARIXTRA by Age

	Age		
	<65 years % (n/N)	**65 to 74 years % (n/N)**	**≥75 years % (n/N)**
Orthopedic surgery[a]	1.8% (23/1,253)	2.2% (24/1,111)	2.7% (33/1,277)
Extended prophylaxis	1.9% (1/52)	1.4% (1/71)	2.9% (6/204)
Abdominal surgery	3.0% (19/644)	3.2% (16/507)	5.0% (14/282)
DVT and PE treatment	0.6% (7/1,151)	1.6% (9/560)	2.1% (12/583)

[a] Includes hip fracture, hip replacement, and knee replacement surgery prophylaxis.

8.6 Renal Impairment

Patients with impaired renal function are at increased risk of bleeding due to reduced clearance of ARIXTRA *[see Contraindications (4) and Warnings and Precautions (5.2)]*. Assess renal function periodically in patients receiving ARIXTRA. Discontinue ARIXTRA immediately

in patients who develop severe renal impairment while on therapy. After discontinuation of ARIXTRA, 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 may persist even longer in patients with renal impairment *[see Clinical Pharmacology (12.4)]*.

8.7 Hepatic Impairment

Following a single, subcutaneous dose of 7.5 mg of ARIXTRA in patients with moderate hepatic impairment (Child-Pugh Category B) compared to subjects with normal liver function, changes from baseline in aPTT, PT/INR, and antithrombin III were similar in the two groups. However, a higher incidence of hemorrhage was observed in subjects with moderate hepatic impairment than in normal subjects, especially mild hematomas at the blood sampling or injection site. The pharmacokinetics of fondaparinux have not been studied in patients with severe hepatic impairment. *[See Dosage and Administration (2.4) and Clinical Pharmacology (12.4).]*

10 OVERDOSAGE

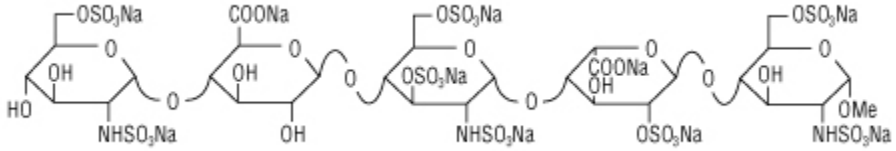
There is no known antidote for ARIXTRA. Overdose of ARIXTRA may lead to hemorrhagic complications. Discontinue treatment and initiate appropriate therapy if bleeding complications associated with overdosage occur.

Data obtained in patients undergoing chronic intermittent hemodialysis suggest that clearance of ARIXTRA can increase by 20% during hemodialysis.

11 DESCRIPTION

ARIXTRA (fondaparinux sodium) Injection is a sterile solution containing fondaparinux sodium. It is a synthetic and specific inhibitor of activated Factor X (Xa). Fondaparinux sodium is methyl O-2-deoxy-6-O-sulfo-2-(sulfoamino)-α-D-glucopyranosyl-(1→4)-O-β-D-glucopyranuronosyl-(1→4)-O-2-deoxy-3,6-di-O-sulfo-2-(sulfoamino)-α-D-glucopyranosyl-(1→4)-O-2-O-sulfo-α-L-idopyranuronosyl-(1→4)-2-deoxy-6-O-sulfo-2-(sulfoamino)-α-D-glucopyranoside, decasodium salt.

The molecular formula of fondaparinux sodium is $C_{31}H_{43}N_3Na_{10}O_{49}S_8$ and its molecular weight is 1728. The structural formula is provided below:



ARIXTRA is supplied as a sterile, preservative-free injectable solution for subcutaneous use.

Each single-dose, prefilled syringe of ARIXTRA, affixed with an automatic needle protection system, contains 2.5 mg of fondaparinux sodium in 0.5 mL, 5.0 mg of fondaparinux sodium in 0.4 mL, 7.5 mg of fondaparinux sodium in 0.6 mL, or 10.0 mg of fondaparinux

sodium in 0.8 mL of an isotonic solution of sodium chloride and water for injection. The final drug product is a clear and colorless to slightly yellow liquid with a pH between 5.0 and 8.0.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The antithrombotic activity of fondaparinux sodium is the result of antithrombin III (ATIII)-mediated selective inhibition of Factor Xa. By selectively binding to ATIII, fondaparinux sodium potentiates (about 300 times) the innate neutralization of Factor Xa by ATIII. Neutralization of Factor Xa interrupts the blood coagulation cascade and thus inhibits thrombin formation and thrombus development.

Fondaparinux sodium does not inactivate thrombin (activated Factor II) and has no known effect on platelet function. At the recommended dose, fondaparinux sodium does not affect fibrinolytic activity or bleeding time.

12.2 Pharmacodynamics

Anti-Xa Activity: The pharmacodynamics/pharmacokinetics of fondaparinux sodium 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 LMWH are not appropriate for this use.) As a result, the activity of fondaparinux sodium is expressed as milligrams (mg) of the fondaparinux calibrator. The anti-Xa activity of the drug increases with increasing drug concentration, reaching maximum values in approximately three hours.

12.3 Pharmacokinetics

Absorption: Fondaparinux sodium administered by subcutaneous injection is rapidly and completely absorbed (absolute bioavailability is 100%). Following a single subcutaneous dose of fondaparinux sodium 2.5 mg in young male subjects, C_{max} of 0.34 mg/L is reached in approximately 2 hours. In patients undergoing treatment with fondaparinux sodium injection 2.5 mg, once daily, 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 fondaparinux sodium injection 5 mg (body weight <50 kg), 7.5 mg (body weight 50 to 100 kg), and 10 mg (body weight >100 kg) 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 sodium distributes mainly in blood and only to a minor extent in extravascular fluid as evidenced by steady state and non-steady state apparent volume of distribution of 7 to 11 L. Similar fondaparinux distribution occurs in patients undergoing elective hip surgery or hip fracture surgery. *In vitro,* fondaparinux sodium 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: In individuals with normal kidney function, fondaparinux is eliminated in urine mainly as unchanged drug. In healthy individuals up to 75 years of age, up to 77% of a single subcutaneous or intravenous fondaparinux dose is eliminated in urine as unchanged drug in 72 hours. The elimination half-life is 17 to 21 hours.

12.4 Special 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 (CrCl 50 to 80 mL/min), approximately 40% lower in patients with moderate renal impairment (CrCl 30 to 50 mL/min), and approximately 55% lower in patients with severe renal impairment (<30 mL/min) compared to patients with normal renal function. A similar relationship between fondaparinux clearance and extent of renal impairment was observed in DVT treatment patients. *[See Contraindications (4) and Warnings and Precautions (5.2).]*

Hepatic Impairment: Following a single, subcutaneous dose of 7.5 mg of ARIXTRA in patients with moderate hepatic impairment (Child-Pugh Category B), C_{max} and AUC were decreased by 22% and 39%, respectively, compared to subjects with normal liver function. The changes from baseline in pharmacodynamic parameters, such as aPTT, PT/INR, and antithrombin III, were similar in normal subjects and in patients with moderate hepatic impairment. Based on these data, no dosage adjustment is recommended in these patients. However, a higher incidence of hemorrhage was observed in subjects with moderate hepatic impairment than in normal subjects *[see Use in Specific Populations (8.7)]*. The pharmacokinetics of fondaparinux have not been studied in patients with severe hepatic impairment. *[See Dosage and Administration (2.4).]*

Pediatric: The pharmacokinetics of fondaparinux have not been investigated in pediatric patients. *[See Contraindications (4), Warnings and Precautions (5.3), and Pediatric Use (8.4).]*

Geriatric: Fondaparinux elimination is prolonged in patients older than 75 years. In studies evaluating fondaparinux sodium 2.5 mg prophylaxis in hip fracture surgery or elective hip surgery, the total clearance of fondaparinux was approximately 25% lower in patients older than 75 years as compared to patients younger than 65 years. A similar relationship between fondaparinux clearance and age was observed in DVT treatment patients. *[See Use in Specific Populations (8.5).]*

Patients Weighing Less Than 50 kg: Total clearance of fondaparinux sodium is decreased by approximately 30% in patients weighing less than 50 kg *[see Dosage and Administration (2.3) and Contraindications (4)]*.

Gender: The pharmacokinetic properties of fondaparinux sodium are not significantly affected by gender.

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 orthopedic surgery.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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.

At subcutaneous doses up to 10 mg/kg/day (about 32 times the recommended human dose based on body surface area), fondaparinux sodium was found to have no effect on fertility and reproductive performance of male and female rats.

14 CLINICAL STUDIES

14.1 Prophylaxis of Thromboembolic Events Following Hip Fracture Surgery

In a randomized, double-blind, clinical trial in patients undergoing hip fracture surgery, ARIXTRA 2.5 mg SC once daily was compared to enoxaparin sodium 40 mg SC once daily, which is not approved for use in patients undergoing hip fracture surgery. A total of 1,711 patients were randomized and 1,673 were treated. Patients ranged in age from 17 to 101 years (mean age 77 years) with 25% men and 75% women. Patients were 99% Caucasian, 1% other races. Patients with multiple traumas affecting more than one organ system, serum creatinine level more than 2 mg/dL (180 micromol/L), or platelet count less than 100,000/mm^3 were excluded from the trial. ARIXTRA was initiated after surgery in 88% of patients (mean 6 hours) and enoxaparin sodium was initiated after surgery in 74% of patients (mean 18 hours). For both drugs, treatment was continued for 7 ± 2 days. The primary efficacy endpoint, venous thromboembolism (VTE), was a composite of documented deep vein thrombosis (DVT) and/or documented symptomatic pulmonary embolism (PE) reported up to Day 11. The efficacy data are provided in Table 7 and demonstrate that under the conditions of the trial ARIXTRA was associated with a VTE rate of 8.3% compared with a VTE rate of 19.1% for enoxaparin sodium for a relative risk reduction of 56% (95% CI: 39%, 70%; P <0.001). Major bleeding episodes occurred in 2.2% of patients receiving ARIXTRA and 2.3% of enoxaparin sodium patients *[see Adverse Reactions (6.1)]*.

Table 7. Efficacy of ARIXTRA in the Peri-operative Prophylaxis of Thromboembolic Events Following Hip Fracture Surgery

Endpoint	Peri-operative Prophylaxis (Day 1 to Day 7 ± 2 post-surgery)			
	ARIXTRA 2.5 mg SC once daily		Enoxaparin Sodium 40 mg SC once daily	
	n/N[a]	% (95% CI)	n/N[a]	% (95% CI)
VTE	52/626	8.3%[b] (6.3, 10.8)	119/624	19.1% (16.1, 22.4)
All DVT	49/624	7.9%[b] (5.9, 10.2)	117/623	18.8% (15.8, 22.1)
Proximal DVT	6/650	0.9%[b] (0.3, 2.0)	28/646	4.3% (2.9, 6.2)
Symptomatic PE	3/831	0.4%[c] (0.1, 1.1)	3/840	0.4% (0.1, 1.0)

[a] N = all evaluable hip fracture surgery patients. Evaluable patients were those who were treated and underwent the appropriate surgery (i.e., hip fracture surgery of the upper third of the femur), with an adequate efficacy assessment up to Day 11.

[b] *P* value versus enoxaparin sodium <0.001.

[c] *P* value versus enoxaparin sodium: NS.

14.2 Extended Prophylaxis of Thromboembolic Events Following Hip Fracture Surgery

In a noncomparative, unblinded manner, 737 patients undergoing hip fracture surgery were initially treated during the peri-operative period with ARIXTRA 2.5 mg once daily for 7 ± 1 days. Eighty-one (81) of the 737 patients were not eligible for randomization into the 3-week double-blind period. Three hundred twenty-six (326) patients and 330 patients were randomized to receive ARIXTRA 2.5 mg once daily or placebo, respectively, in or out of the hospital for 21 ± 2 days. Patients ranged in age from 23 to 96 years (mean age 75 years) and were 29% men and 71% women. Patients were 99% Caucasian and 1% other races. Patients with multiple traumas affecting more than one organ system or serum creatinine level more than 2 mg/dL (180 micromol/L) were excluded from the trial. The primary efficacy endpoint, venous thromboembolism (VTE), was a composite of documented deep vein thrombosis (DVT) and/or documented symptomatic pulmonary embolism (PE) reported for up to 24 days following randomization. The efficacy data are provided in Table 8 and demonstrate that extended prophylaxis with ARIXTRA was associated with a VTE rate of 1.4% compared with a VTE rate of 35.0% for placebo for a relative risk reduction of 95.9% (95% CI = [98.7; 87.1], *P* <0.0001). Major bleeding rates during the 3-week extended prophylaxis period for ARIXTRA occurred in 2.4% of patients receiving ARIXTRA and 0.6% of placebo-treated patients *[see Adverse Reactions (6.1)]*.

Table 8. Efficacy of ARIXTRA Injection in the Extended Prophylaxis of Thromboembolic Events Following Hip Fracture Surgery

Endpoint	Extended Prophylaxis (Day 8 to Day 28 ± 2 post-surgery)			
	ARIXTRA 2.5 mg SC once daily		Placebo SC once daily	
	n/N[a]	% (95% CI)	n/N[a]	% (95% CI)
VTE	3/208	1.4%[b] (0.3, 4.2)	77/220	35.0% (28.7, 41.7)
All DVT	3/208	1.4%[b] (0.3, 4.2)	74/218	33.9% (27.7, 40.6)
Proximal DVT	2/221	0.9%[b] (0.1, 3.2)	35/222	15.8% (11.2, 21.2)
Symptomatic VTE (all)	1/326	0.3%[c] (0.0, 1.7)	9/330	2.7% (1.3, 5.1)
Symptomatic PE	0/326	0.0%[d] (0.0, 1.1)	3/330	0.9% (0.2, 2.6)

[a] N = all randomized evaluable hip fracture surgery patients. Evaluable patients were those who were treated in the post-randomization period, with an adequate efficacy assessment for up to 24 days following randomization.

[b] *P* value versus placebo <0.001

[c] *P* value versus placebo = 0.021.

[d] *P* value versus placebo = NS.

14.3 Prophylaxis of Thromboembolic Events Following Hip Replacement Surgery

In 2 randomized, double-blind, clinical trials in patients undergoing hip replacement surgery, ARIXTRA 2.5 mg SC once daily was compared to either enoxaparin sodium 30 mg SC every 12 hours (Study 1) or to enoxaparin sodium 40 mg SC once a day (Study 2). In Study 1, a total of 2,275 patients were randomized and 2,257 were treated. Patients ranged in age from 18 to 92 years (mean age 65 years) with 48% men and 52% women. Patients were 94% Caucasian, 4% black, <1% Asian, and 2% others. In Study 2, a total of 2,309 patients were randomized and 2,273 were treated. Patients ranged in age from 24 to 97 years (mean age 65 years) with 42% men and 58% women. Patients were 99% Caucasian, and 1% other races. Patients with serum creatinine level more than 2 mg/dL (180 micromol/L), or platelet count less than 100,000/mm^3 were excluded from both trials. In Study 1, ARIXTRA was initiated 6 ± 2 hours (mean 6.5 hours) after surgery in 92% of patients and enoxaparin sodium was initiated 12 to 24 hours (mean 20.25 hours) after surgery in 97% of patients. In Study 2, ARIXTRA was initiated 6 ± 2 hours (mean 6.25 hours) after surgery in 86% of patients and enoxaparin sodium was initiated 12 hours before surgery in 78% of patients. The first post-operative enoxaparin sodium dose was given within 12 hours after surgery in 60% of patients and 12 to 24 hours after surgery in 35% of patients with a mean of 13 hours. For both studies, both study treatments were continued for 7 ± 2 days. The efficacy data are provided in Table 9. Under the conditions of Study 1, ARIXTRA was associated with a VTE rate of 6.1% compared with a VTE rate of 8.3% for enoxaparin sodium for a relative risk reduction of 26% (95% CI: -11%, 53%; *P* = NS). Under the

conditions of Study 2, fondaparinux sodium was associated with a VTE rate of 4.1% compared with a VTE rate of 9.2% for enoxaparin sodium for a relative risk reduction of 56% (95% CI: 33%, 73%; *P* <0.001). For the 2 studies combined, the major bleeding episodes occurred in 3.0% of patients receiving ARIXTRA and 2.1% of enoxaparin sodium patients *[see Adverse Reactions (6.1)]*.

Table 9. Efficacy of ARIXTRA in the Prophylaxis of Thromboembolic Events Following Hip Replacement Surgery

	Study 1 n/N[a] % (95% CI)		**Study 2 n/N[a] % (95% CI)**	
Endpoint	**ARIXTRA 2.5 mg SC once daily**	**Enoxaparin Sodium 30 mg SC every 12 hr**	**ARIXTRA 2.5 mg SC once daily**	**Enoxaparin Sodium 40 mg SC once daily**
VTE[b]	48/787 6.1%[c] (4.5, 8.0)	66/797 8.3% (6.5, 10.4)	37/908 4.1%[e] (2.9, 5.6)	85/919 9.2% (7.5, 11.3)
All DVT	44/784 5.6%[d] (4.1, 7.5)	65/796 8.2% (6.4, 10.3)	36/908 4.0%[e] (2.8, 5.4)	83/918 9.0% (7.3, 11.1)
Proximal DVT	14/816 1.7%[c] (0.9, 2.9)	10/830 1.2% (0.6, 2.2)	6/922 0.7%[f] (0.2, 1.4)	23/927 2.5% (1.6, 3.7)
Symptomatic PE	5/1,126 0.4%[c] (0.1, 1.0)	1/1,128 0.1% (0.0, 0.5)	2/1,129 0.2%[c] (0.0, 0.6)	2/1,123 0.2% (0.0, 0.6)

[a] N = all evaluable hip replacement surgery patients. Evaluable patients were those who were treated and underwent the appropriate surgery (i.e., hip replacement surgery), with an adequate efficacy assessment up to Day 11.

[b] VTE was a composite of documented DVT and/or documented symptomatic PE reported up to Day 11.

[c] *P* value versus enoxaparin sodium: NS.

[d] *P* value versus enoxaparin sodium in study 1: <0.05.

[e] *P* value versus enoxaparin sodium in study 2: <0.001.

[f] *P* value versus enoxaparin sodium in study 2: <0.01.

14.4 Prophylaxis of Thromboembolic Events Following Knee Replacement Surgery

In a randomized, double-blind, clinical trial in patients undergoing knee replacement surgery (i.e., surgery requiring resection of the distal end of the femur or proximal end of the tibia), ARIXTRA 2.5 mg SC once daily was compared to enoxaparin sodium 30 mg SC every 12 hours. A total of 1,049 patients were randomized and 1,034 were treated. Patients ranged in age from 19 to 94 years (mean age 68 years) with 41% men and 59% women. Patients were 88%

Caucasian, 8% black, <1% Asian, and 3% others. Patients with serum creatinine level more than 2 mg/dL (180 micromol/L), or platelet count less than 100,000/mm^3 were excluded from the trial. ARIXTRA was initiated 6 ± 2 hours (mean 6.25 hours) after surgery in 94% of patients, and enoxaparin sodium was initiated 12 to 24 hours (mean 21 hours) after surgery in 96% of patients. For both drugs, treatment was continued for 7 ± 2 days. The efficacy data are provided in Table 10 and demonstrate that under the conditions of the trial, ARIXTRA was associated with a VTE rate of 12.5% compared with a VTE rate of 27.8% for enoxaparin sodium for a relative risk reduction of 55% (95% CI: 36%, 70%; *P* <0.001). Major bleeding episodes occurred in 2.1% of patients receiving ARIXTRA and 0.2% of enoxaparin sodium patients *[see Adverse Reactions (6.1)]*.

Table 10. Efficacy of ARIXTRA in the Prophylaxis of Thromboembolic Events Following Knee Replacement Surgery

Endpoint	ARIXTRA 2.5 mg SC once daily		Enoxaparin Sodium 30 mg SC every 12 hours	
	n/N[a]	% (95% CI)	n/N[a]	% (95% CI)
VTE[b]	45/361	12.5%[c] (9.2, 16.3)	101/363	27.8% (23.3, 32.7)
All DVT	45/361	12.5%[c] (9.2, 16.3)	98/361	27.1% (22.6, 32.0)
Proximal DVT	9/368	2.4%[d] (1.1, 4.6)	20/372	5.4% (3.3, 8.2)
Symptomatic PE	1/517	0.2%[d] (0.0, 1.1)	4/517	0.8% (0.2, 2.0)

[a] N = all evaluable knee replacement surgery patients. Evaluable patients were those who were treated and underwent the appropriate surgery (i.e., knee replacement surgery), with an adequate efficacy assessment up to Day 11.

[b] VTE was a composite of documented DVT and/or documented symptomatic PE reported up to Day 11.

[c] *P* value versus enoxaparin sodium <0.001.

[d] *P* value versus enoxaparin sodium: NS.

14.5 Prophylaxis of Thromboembolic Events Following Abdominal Surgery in Patients at Risk for Thromboembolic Complications

Abdominal surgery patients at risk included the following: Those undergoing surgery under general anesthesia lasting longer than 45 minutes who are older than 60 years with or without additional risk factors; and those undergoing surgery under general anesthesia lasting longer than 45 minutes who are older than 40 years with additional risk factors. Risk factors included neoplastic disease, obesity, chronic obstructive pulmonary disease, inflammatory bowel disease, history of deep vein thrombosis (DVT) or pulmonary embolism (PE), or congestive heart failure.

In a randomized, double-blind, clinical trial in patients undergoing abdominal surgery, ARIXTRA 2.5 mg SC once daily started postoperatively was compared to dalteparin sodium 5,000 IU SC once daily, with one 2,500 IU SC preoperative injection and a 2,500 IU SC first

postoperative injection. A total of 2,927 patients were randomized and 2,858 were treated. Patients ranged in age from 17 to 93 years (mean age 65 years) with 55% men and 45% women. Patients were 97% Caucasian, 1% black, 1% Asian, and 1% others. Patients with serum creatinine level more than 2 mg/dL (180 micromol/L), or platelet count less than 100,000/mm^3 were excluded from the trial. Sixty-nine percent (69%) of study patients underwent cancer-related abdominal surgery. Study treatment was continued for 7 ± 2 days. The efficacy data are provided in Table 11 and demonstrate that prophylaxis with ARIXTRA was associated with a VTE rate of 4.6% compared with a VTE rate of 6.1% for dalteparin sodium (*P* = NS).

Table 11. Efficacy of ARIXTRA In Prophylaxis of Thromboembolic Events Following Abdominal Surgery

Endpoint	ARIXTRA 2.5 mg SC once daily		Dalteparin Sodium 5,000 IU SC once daily	
	n/N[a]	% (95% CI)	n/N[a]	% (95% CI)
VTE[b]	47/1,027	4.6%[c] (3.4, 6.0)	62/1,021	6.1% (4.7, 7.7)
All DVT	43/1,024	4.2% (3.1, 5.6)	59/1,018	5.8% (4.4, 7.4)
Proximal DVT	5/1,076	0.5% (0.2, 1.1)	5/1,077	0.5% (0.2, 1.1)
Symptomatic VTE	6/1,465	0.4% (0.2, 0.9)	5/1,462	0.3% (0.1, 0.8)

[a] N = all evaluable abdominal surgery patients. Evaluable patients were those who were randomized and had an adequate efficacy assessment up to Day 10; non-treated patients and patients who did not undergo surgery did not get a VTE assessment.

[b] VTE was a composite of venogram positive DVT, symptomatic DVT, non-fatal PE and/or fatal PE reported up to Day 10.

[c] *P* value versus dalteparin sodium: NS.

14.6 Treatment of Deep Vein Thrombosis

In a randomized, double-blind, clinical trial in patients with a confirmed diagnosis of acute symptomatic DVT without PE, ARIXTRA 5 mg (body weight <50 kg), 7.5 mg (body weight 50 to 100 kg), or 10 mg (body weight >100 kg) SC once daily (ARIXTRA treatment regimen) was compared to enoxaparin sodium 1 mg/kg SC every 12 hours. Almost all patients started study treatment in hospital. Approximately 30% of patients in both groups were discharged home from the hospital while receiving study treatment. A total of 2,205 patients were randomized and 2,192 were treated. Patients ranged in age from 18 to 95 years (mean age 61 years) with 53% men and 47% women. Patients were 97% Caucasian, 2% black, and 1% other races. Patients with serum creatinine level more than 2 mg/dL (180 micromol/L), or platelet count less than 100,000/mm^3 were excluded from the trial. For both groups, treatment continued for at least 5 days with a treatment duration range of 7 ± 2 days, and both treatment groups received vitamin K antagonist therapy initiated within 72 hours after the first study drug administration and continued for 90 ± 7 days, with regular dose adjustments to achieve an INR

of 2 to 3. The primary efficacy endpoint was confirmed, symptomatic, recurrent VTE reported up to Day 97. The efficacy data are provided in Table 12.

Table 12. Efficacy of ARIXTRA in the Treatment of Deep Vein Thrombosis (All Randomized)

Endpoint	ARIXTRA 5, 7.5, or 10 mg SC once daily N = 1,098		Enoxaparin Sodium 1 mg/kg SC every 12 hours N = 1,107	
	n	% (95% CI)	n	% (95% CI)
Total VTE[a]	43	3.9% (2.8, 5.2)	45	4.1% (3.0, 5.4)
DVT only	18	1.6% (1.0, 2.6)	28	2.5% (1.7, 3.6)
Non-fatal PE	20	1.8% (1.1, 2.8)	12	1.1% (0.6, 1.9)
Fatal PE	5	0.5% (0.1, 1.1)	5	0.5% (0.1, 1.1)

[a] VTE was a composite of symptomatic recurrent non-fatal VTE or fatal PE reported up to Day 97. The 95% confidence interval for the treatment difference for total VTE was: (-1.8% to 1.5%).

During the initial treatment period, 18 (1.6%) of patients treated with fondaparinux sodium and 10 (0.9%) of patients treated with enoxaparin sodium had a VTE endpoint (95% CI for the treatment difference [fondaparinux sodium-enoxaparin sodium] for VTE rates: -0.2%; 1.7%).

14.7 Treatment of Pulmonary Embolism

In a randomized, open-label, clinical trial in patients with a confirmed diagnosis of acute symptomatic PE, with or without DVT, ARIXTRA 5 mg (body weight <50 kg), 7.5 mg (body weight 50 to 100 kg), or 10 mg (body weight >100 kg) SC once daily (ARIXTRA treatment regimen) was compared to heparin IV bolus (5,000 USP units) followed by a continuous IV infusion adjusted to maintain 1.5 to 2.5 times aPTT control value. Patients with a PE requiring thrombolysis or surgical thrombectomy were excluded from the trial. All patients started study treatment in hospital. Approximately 15% of patients were discharged home from the hospital while receiving ARIXTRA therapy. A total of 2,213 patients were randomized and 2,184 were treated. Patients ranged in age from 18 to 97 years (mean age 62 years) with 44% men and 56% women. Patients were 94% Caucasian, 5% black, and 1% other races. Patients with serum creatinine level more than 2 mg/dL (180 micromol/L), or platelet count less than 100,000/mm^3 were excluded from the trial. For both groups, treatment continued for at least 5 days with a treatment duration range 7 ± 2 days, and both treatment groups received vitamin K antagonist therapy initiated within 72 hours after the first study drug administration and continued for 90 ± 7 days, with regular dose adjustments to achieve an INR of 2 to 3. The primary efficacy endpoint was confirmed, symptomatic, recurrent VTE reported up to Day 97. The efficacy data are provided in Table 13.

Table 13. Efficacy of ARIXTRA in the Treatment of Pulmonary Embolism (All Randomized)

Endpoint	ARIXTRA 5, 7.5, or 10 mg SC once daily N = 1,103		Heparin aPTT adjusted IV N = 1,110	
	n	% (95% CI)	n	% (95% CI)
Total VTE[a]	42	3.8% (2.8, 5.1)	56	5.0% (3.8, 6.5)
DVT only	12	1.1% (0.6, 1.9)	17	1.5% (0.9, 2.4)
Non-fatal PE	14	1.3% (0.7, 2.1)	24	2.2% (1.4, 3.2)
Fatal PE	16	1.5% (0.8, 2.3)	15	1.4% (0.8, 2.2)

[a] VTE was a composite of symptomatic recurrent non-fatal VTE or fatal PE reported up to Day 97. The 95% confidence interval for the treatment difference for total VTE was: (-3.0% to 0.5%).

During the initial treatment period, 12 (1.1%) of patients treated with fondaparinux sodium and 19 (1.7%) of patients treated with heparin had a VTE endpoint (95% CI for the treatment difference [fondaparinux sodium-heparin] for VTE rates: -1.6%; 0.4%).

16 HOW SUPPLIED/STORAGE AND HANDLING

ARIXTRA Injection is available in the following strengths and package sizes:

2.5 mg ARIXTRA in 0.5 mL single-dose prefilled syringe, affixed with a 27-gauge x ½-inch needle and an automatic needle protection system with white plunger rod.

NDC 0007-3230-02 2 Single Unit Syringes
NDC 0007-3230-11 10 Single Unit Syringes

5 mg ARIXTRA in 0.4 mL single-dose prefilled syringe, affixed with a 27-gauge x ½-inch needle and an automatic needle protection system with white plunger rod.

NDC 0007-3232-11 10 Single Unit Syringes

7.5 mg ARIXTRA in 0.6 mL single-dose prefilled syringe, affixed with a 27-gauge x ½-inch needle and an automatic needle protection system with white plunger rod.

NDC 0007-3234-02 2 Single Unit Syringes
NDC 0007-3234-11 10 Single Unit Syringes

10 mg ARIXTRA in 0.8 mL single-dose prefilled syringe, affixed with a 27-gauge x ½-inch needle and an automatic needle protection system with white plunger rod.

NDC 0007-3236-02 2 Single Unit Syringes
NDC 0007-3236-11 10 Single Unit Syringes

Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F).

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (17.2)

17.1 Patient Advice

If the patients have had neuraxial anesthesia or spinal puncture, and particularly, if they are taking concomitant NSAIDS, platelet inhibitors, or other anticoagulants, they should be informed to watch for signs and symptoms of spinal or epidural hematomas, such as tingling, numbness (especially in the lower limbs) and muscular weakness. If any of these symptoms occur, the patients should contact his or her physician immediately.

The use of aspirin and other NSAIDS may enhance the risk of hemorrhage. Their use should be discontinued prior to ARIXTRA therapy whenever possible; if co-administration is essential, the patient's clinical and laboratory status should be closely monitored. *[See Drug Interactions (7).]*

If patients must self-administer ARIXTRA (e.g., if ARIXTRA is used at home), they should be advised of the following:

- ARIXTRA should be given by subcutaneous injection. Patients must be instructed in the proper technique for administration.
- As with all anticoagulants, the most important risk with ARIXTRA administration is bleeding. Patients should be counseled on signs and symptoms of possible bleeding.
- It may take them longer than usual to stop bleeding.
- They may bruise and/or bleed more easily when they are treated with ARIXTRA.
- They should report any unusual bleeding, bruising, or signs of thrombocytopenia (such as a rash of dark red spots under the skin) to their physician *[see Warnings and Precautions (5.1, 5.4)]*.
- To tell their physicians and dentists they are taking ARIXTRA and/or any other product known to affect bleeding before any surgery is scheduled and before any new drug is taken *[see Warnings and Precautions (5.1)]*.
- To tell their physicians and dentists of all medications they are taking, including those obtained without a prescription, such as aspirin or other NSAIDs. *[See Drug Interactions (7).]*

Keep out of the reach of children.

17.2 FDA-Approved Patient Labeling

Patient labeling is provided as a tear-off leaflet at the end of this full prescribing information.

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

GlaxoSmithKline
Research Triangle Park, NC 27709

ARX:10PI

PHARMACIST-DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT

PATIENT INFORMATION
ARIXTRA® (Ah-RIX-trah)
fondaparinux sodium injection

Read the Patient Information that comes with ARIXTRA before you start taking it and each time you get a refill. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about ARIXTRA, ask your doctor or pharmacist.

What is the most important information I should know about ARIXTRA?
Certain medical procedures involving the spine, such as an epidural (pain medication given through the spine), spinal anesthesia, or spinal puncture, may be used during your hospital stay. If you need any of these procedures while receiving ARIXTRA, heparins, heparinoids, or low-molecular weight heparins (anticoagulants), you may be at risk for having a blood clot (hematoma) in or around your spine. This type of clot is very serious, as it can cause long-term and possibly permanent paralysis (loss of the ability to move).

If you receive ARIXTRA after an epidural or spinal anesthetic is used, as the anesthesia for your surgery, your doctor will watch you closely for problems with feeling (sensation) and being able to move. Tell your doctor right away if you have any of these signs and symptoms, especially in your legs and feet:

- tingling
- numbness
- muscle weakness

Because the risk of bleeding may be higher, tell your doctor before taking ARIXTRA if you:

- are also taking certain other medicines that affect blood clotting such as aspirin, an NSAID (for example, ibuprofen or naproxen), clopidogrel, or warfarin sodium.
- have bleeding problems.
- had problems in the past with pain medication given through the spine.
- have had surgery to your spine.
- have a spinal deformity.

What is ARIXTRA?

ARIXTRA is a prescription medicine that “thins your blood” (also known as an anticoagulant). ARIXTRA is used to:

- help prevent blood clots from forming in patients who have had certain surgeries of the hip, knee, or the stomach area (abdominal surgery)
- treat people who have blood clots in their legs or blood clots that travel to their lungs

It is not known if ARIXTRA is safe and effective for use in children younger than 18 years of age.

Who should not take ARIXTRA?

Do not take ARIXTRA if you have:

- certain kidney problems
- active bleeding problems
- an infection in your heart
- low platelet counts and if you test positive for a certain antibody while you are taking ARIXTRA
- had a serious allergic reaction to ARIXTRA

People who weigh less than 110 pounds (50 kg) should not use ARIXTRA to prevent blood clots from forming after surgery.

What should I tell my doctor before taking ARIXTRA?

Tell your doctor about all of your medical conditions, including if you:

- have had any bleeding problems (such as stomach ulcers)
- have had a stroke
- have had recent surgeries, including eye surgery
- have diabetic eye disease
- have kidney problems
- have uncontrolled high blood pressure
- have a latex allergy. The packaging (needle guard) for ARIXTRA contains dry natural rubber.
- are pregnant. It is not known if ARIXTRA will harm your unborn baby. If you are pregnant, talk to your doctor about the best way for you to prevent or treat blood clots.
- are breast-feeding. It is not known if ARIXTRA passes into breast milk.

Tell your doctor about all the medicines you take including prescriptions and non-prescription medicines, vitamins, and herbal supplements. Some medicines can increase your risk of bleeding. Especially tell your doctor if you take:

- aspirin
- NSAIDS (such as ibuprofen or naproxen)
- other blood thinner medicines, such as clopidogrel or warfarin

See “What is the most important information I should know about ARIXTRA?” Do not start taking any new medicines without first talking to your doctor.

Know the medicines you take. Tell all your doctors and dentist that you take ARIXTRA, especially if you need to have any kind of surgery or a dental procedure. Keep a list of your medicines and show it to all your doctors and pharmacist before you start a new medicine.

How should I take ARIXTRA?

- Take ARIXTRA exactly as prescribed by your doctor.
- ARIXTRA is given by injection under the skin (subcutaneous injection). See “How should I give an injection of ARIXTRA?”
- If your doctor tells you that you may give yourself injections of ARIXTRA at home, you will be shown how to give the injections first before you do them on your own.
- Tell your doctor if you have any bleeding or bruising while taking ARIXTRA.
- If you miss a dose of ARIXTRA, take your dose as soon as you remember. Do not take 2 doses at the same time.
- If you take too much ARIXTRA, call your doctor right away.
- Do not use ARIXTRA if:
  - the solution appears discolored (the solution should normally appear clear),
  - you see any particles in the solution, or
  - the syringe is damaged.

What are possible side effects of ARIXTRA?

ARIXTRA can cause serious side effects. See “What is the most important information I should know about ARIXTRA?”

- Severe **bleeding**

  Certain conditions can increase your risk for severe bleeding, including:

  -some bleeding problems

  -some gastrointestinal problems including ulcers

  -some types of strokes

-uncontrolled high blood pressure
-diabetic eye disease
-soon after brain, spine, or eye surgery

- **Certain kidney problems can also increase your risk of bleeding with ARIXTRA**. Your doctor may check your kidney function while you are taking ARIXTRA.
- **People undergoing surgery who weigh less than 110 pounds**. See "Who should not take ARIXTRA?"
- **Low blood platelets**. Low blood platelets can happen when you take ARIXTRA. Platelets are blood cells that help your blood to clot normally. Your doctor may check your platelet counts while you take ARIXTRA.
  You may bruise or bleed more easily while taking ARIXTRA, and it may take longer than usual for bleeding to stop.
  Tell your doctor if you have any of these signs or symptoms of bleeding while taking ARIXTRA.
  -any bleeding
  -bruising
  -rash of dark red spots under the skin
- **Allergic reactions (itching, swelling, or rash).** See "What should I tell my doctor before taking ARIXTRA?" Serious allergic reactions can happen when you take ARIXTRA. If you experience swelling of the face or mouth or have difficulty in swallowing or breathing, contact your doctor right away. You should stop ARIXTRA if this happens.

Other side effects include:

- **Injection site reactions**. Bleeding, rash, and itching can happen at the place where you inject ARIXTRA.
- **Low red blood cell counts (anemia).** Your doctor may check your red blood cell counts while you are taking ARIXTRA.
- **Increased liver enzyme test results.** Your doctor may check your liver function while you are taking ARIXTRA.
- **Sleep problems (insomnia)**.

These are not all the possible side effects of ARIXTRA. Call your doctor if you have any side effects that bother you or don't go away.

Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088.

How should I store ARIXTRA?
Store ARIXTRA at room temperature 59°F to 86°F (15°C to 30°C). Do not freeze. Safely, throw away ARIXTRA that is out of date or no longer needed.
Keep ARIXTRA and all medicines out of the reach of children.

General information about ARIXTRA
Medicines are sometimes prescribed for purposes other than those described in patient information leaflets. Do not use ARIXTRA for a condition for which it was not prescribed. Do not give ARIXTRA to other people. It may harm them.

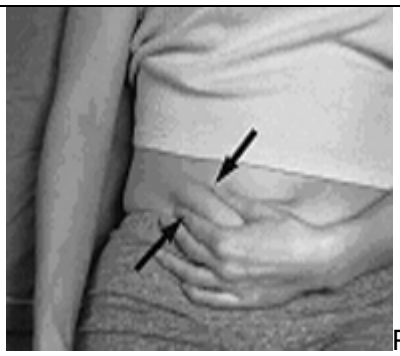
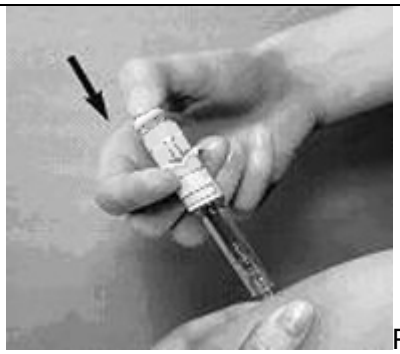
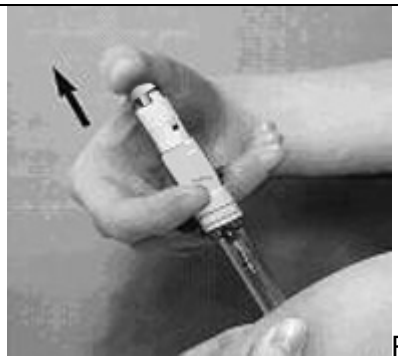
This leaflet summarizes the most important information about ARIXTRA. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about ARIXTRA that is written for healthcare professionals. For more information about ARIXTRA, go to www.ARIXTRA.com or call 1-888-825-5249.

What are the ingredients in ARIXTRA?
Active Ingredient: fondaparinux sodium
Inactive Ingredients: sodium chloride and water for injection

How should I give an injection of ARIXTRA?
ARIXTRA is injected into a skin fold of the lower stomach area (abdomen). Do not inject ARIXTRA into muscle. Usually a doctor or nurse will give this injection to you. In some cases you may be taught how to do this yourself. Be sure that you read, understand, and follow the step-by-step instructions in this leaflet, on how to give yourself an injection of ARIXTRA.

Instructions for self-administration	
The different parts of ARIXTRA safety syringe are:	
1. Rigid needle guard 2. Plunger 3. Finger-grip 4. Security sleeve	

Syringe BEFORE USE	Syringe AFTER USE
	
1. Wash your hands thoroughly with soap and water. Towel dry.	
2. Sit or lie down in a comfortable position. Choose a spot on the lower stomach area (abdomen), at least 2 inches below your belly button (Figure A). Change (alternate) between using the left and right side of the lower abdomen for each injection. If you have any questions talk to your nurse or doctor.	 Figure A.
3. Clean the injection area with an alcohol swab.	
4. Remove the needle guard, by first twisting it and then pulling it in a straight line away from the body of the syringe (Figure B). Discard the needle guard. **To prevent infection, do not touch the needle or let it come in contact with any surface before the injection.** A small air bubble in the syringe is normal. To be sure that you do not lose any medicine from the syringe, do not try to remove air bubbles from the syringe before giving the injection.	 Figure B.

5. Gently pinch the skin that has been cleaned to make a fold. Hold the fold between the thumb and the forefinger of one hand during the entire injection (Figure C).	 Figure C.
6. Hold the syringe firmly in your other hand using the finger grip. Insert the full length of the needle directly up and down (at an angle of 90°) into the skin fold (Figure D).	 Figure D.
7. Inject all of the medicine in the syringe by pressing down on the plunger as far as it goes. This will activate the automatic needle protection system (Figure E).	 Figure E.
8. Release the plunger. The needle will withdraw automatically from the skin, and pull back (retract) into the security sleeve where it will be locked (Figure F).	 Figure F.
Follow the instructions given to you by your nurse or doctor about the right way to throw away used syringes and needles. There may be state laws about the right way to dispose of used syringes, needles, and disposal containers.	

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