

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)

xx/xxxx

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 7 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)

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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)

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1 FULL PRESCRIBING INFORMATION

2 **WARNING: SPINAL/EPIDURAL HEMATOMAS**

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

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

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

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

19 **1 INDICATIONS AND USAGE**

20 **1.1 Prophylaxis of Deep Vein Thrombosis**

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

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

27 **1.2 Treatment of Acute Deep Vein Thrombosis**

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

30 **1.3 Treatment of Acute Pulmonary Embolism**

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

34 **2 DOSAGE AND ADMINISTRATION**

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

37 **2.1 Deep Vein Thrombosis Prophylaxis Following Hip Fracture, Hip**
38 **Replacement, and Knee Replacement Surgery**

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

45 In patients undergoing hip fracture surgery, an extended prophylaxis course of up to
46 24 additional days is recommended. In patients undergoing hip fracture surgery, a total of
47 32 days (peri-operative and extended prophylaxis) was administered in clinical trials. [*See*
48 *Warnings and Precautions (5.6), Adverse Reactions (6), and Clinical Studies (14)*].

49 **2.2 Deep Vein Thrombosis Prophylaxis Following Abdominal Surgery**

50 In patients undergoing abdominal surgery, the recommended dose of ARIXTRA is
51 2.5 mg administered by subcutaneous injection once daily after hemostasis has been established.
52 Administer the initial dose no earlier than 6 to 8 hours after surgery. Administration of
53 ARIXTRA earlier than 6 hours after surgery increases the risk of major bleeding. The usual
54 duration of administration is 5 to 9 days, and up to 10 days of ARIXTRA was administered in
55 clinical trials.

56 **2.3 Deep Vein Thrombosis and Pulmonary Embolism Treatment**

57 In patients with acute symptomatic DVT and in patients with acute symptomatic PE, the
58 recommended dose of ARIXTRA is 5 mg (body weight <50 kg), 7.5 mg (body weight 50 to
59 100 kg), or 10 mg (body weight >100 kg) by subcutaneous injection once daily (ARIXTRA
60 treatment regimen). Initiate concomitant treatment with warfarin sodium as soon as possible,
61 usually within 72 hours. Continue treatment with ARIXTRA for at least 5 days and until a
62 therapeutic oral anticoagulant effect is established (INR 2 to 3). The usual duration of
63 administration of ARIXTRA is 5 to 9 days; up to 26 days of ARIXTRA injection was
64 administered in clinical trials. [*See Warnings and Precautions (5.6), Adverse Reactions (6), and*
65 *Clinical Studies (14)*].

66 **2.4 Hepatic Impairment**

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

72 **2.5 Instructions for Use**

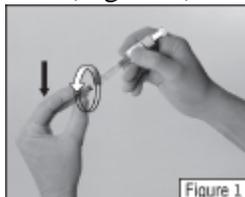
73 ARIXTRA Injection is provided in a single-dose, prefilled syringe affixed with an
74 automatic needle protection system. ARIXTRA is administered by subcutaneous injection. It
75 must not be administered by intramuscular injection. ARIXTRA is intended for use under a
76 physician's guidance. Patients may self-inject only if their physician determines that it is
77 appropriate and the patients are trained in subcutaneous injection techniques.

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

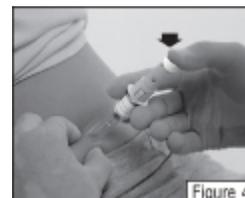
80 **To avoid the loss of drug when using the prefilled syringe, do not expel the air**
81 **bubble from the syringe before the injection.** Administration should be made in the fatty
82 tissue, alternating injection sites (e.g., between the left and right anterolateral or the left and right
83 posterolateral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

84 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).



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).



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.

85 **3 DOSAGE FORMS AND STRENGTHS**

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

88 **4 CONTRAINDICATIONS**

89 ARIXTRA is contraindicated in the following conditions:

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

100 **5 WARNINGS AND PRECAUTIONS**

101 **5.1 Hemorrhage**

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

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

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

116 **5.2 Renal Impairment and Bleeding Risk**

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

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

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

125
126 **Table 1. Incidence of Major Bleeding in Patients Treated With ARIXTRA by Renal**
127 **Function Status for Surgical Prophylaxis and Treatment of Deep Vein Thrombosis (DVT)**
128 **and Pulmonary Embolism (PE)**

Population	Timing of Dose	Degree of Renal Impairment			
		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)

129 CrCl = creatinine clearance.

130 ^a Hip fracture, hip replacement, and knee replacement surgery prophylaxis.

131
132 Assess renal function periodically in patients receiving ARIXTRA. Discontinue the drug
133 immediately in patients who develop severe renal impairment while on therapy. After
134 discontinuation of ARIXTRA, its anticoagulant effects may persist for 2 to 4 days in patients
135 with normal renal function (i.e., at least 3 to 5 half-lives). The anticoagulant effects of
136 ARIXTRA may persist even longer in patients with renal impairment [see *Clinical*
137 *Pharmacology (12.4)*].

138 **5.3 Body Weight <50 Kg and Bleeding Risk**

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

- 141 In patients who weigh less than 50 kg:
- 142 • Do not administer ARIXTRA as prophylactic therapy for patients undergoing hip fracture,
 - 143 hip replacement, or knee replacement surgery and abdominal surgery [see *Contraindications*
 - 144 (4)].
 - 145 • Use ARIXTRA with caution in the treatment of PE and DVT.

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

152 **5.4 Thrombocytopenia**

153 Thrombocytopenia can occur with the administration of ARIXTRA. Thrombocytopenia
154 of any degree should be monitored closely. Discontinue ARIXTRA if the platelet count falls
155 below 100,000/mm³. Moderate thrombocytopenia (platelet counts between 100,000/mm³ and
156 50,000/mm³) occurred at a rate of 3.0% in patients given ARIXTRA 2.5 mg in the peri-operative
157 hip fracture, hip replacement, or knee replacement surgery and abdominal surgery clinical trials.
158 Severe thrombocytopenia (platelet counts less than 50,000/mm³) occurred at a rate of 0.2% in
159 patients given ARIXTRA 2.5 mg in these clinical trials. During extended prophylaxis, no cases
160 of moderate or severe thrombocytopenia were reported.

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

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

168 **5.5 Neuraxial Anesthesia and Post-operative Indwelling Epidural Catheter Use**

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

178 **5.6 Monitoring: Laboratory Tests**

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

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

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

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

192 **5.7 Latex**

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

195 **6 ADVERSE REACTIONS**

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

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

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

- 204 • 2 peri-operative dose-response trials (n = 989)
- 205 • 4 active-controlled peri-operative VTE prophylaxis trials with enoxaparin sodium
206 (n = 3,616), an extended VTE prophylaxis trial (n = 327), and an active-controlled trial with
207 dalteparin sodium (n = 1,425)
- 208 • a dose-response trial (n = 111) and an active-controlled trial with enoxaparin sodium in DVT
209 treatment (n = 1,091)
- 210 • an active-controlled trial with heparin in PE treatment (n = 1,092)

211 **6.1 Hemorrhage**

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

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

217

218 **Table 2. Bleeding Across Randomized, Controlled Hip Fracture, Hip Replacement, and**
 219 **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%)

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

221 ^b Not approved for use in patients undergoing hip fracture surgery.

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

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

228 ^e Minor bleeding was defined as clinically overt bleeding that was not major.

229

230 A separate analysis of major bleeding across all randomized, controlled, peri-operative,
 231 prophylaxis clinical studies of hip fracture, hip replacement, or knee replacement surgery
 232 according to the time of the first injection of ARIXTRA after surgical closure was performed in
 233 patients who received ARIXTRA only post-operatively. In this analysis, the incidences of major
 234 bleeding were as follows: <4 hours was 4.8% (5/104), 4 to 6 hours was 2.3% (28/1,196), 6 to
 235 8 hours was 1.9% (38/1,965). In all studies, the majority (≥75%) of the major bleeding events
 236 occurred during the first 4 days after surgery.

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

240

241 **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%)

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

246 ^b Minor bleeding was defined as clinically overt bleeding that was not major.

247

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

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

253

254 **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%)

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

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

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

264 ^d Minor bleeding was defined as clinically overt bleeding that was not major.

265
 266 **6.2 Local Reactions**

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

269 **6.3 Elevations of Serum Aminotransferases**

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

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

281 comparison, these increases were reported in 4.8% and 12.3% of patients, respectively, in the
 282 DVT treatment trial during treatment with enoxaparin sodium 1 mg/kg every 12 hours and in
 283 2.9% and 8.7% of patients, respectively, in the PE treatment trial during treatment with aPTT
 284 adjusted heparin.

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

288 **6.4 Other Adverse Reactions**

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

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

Adverse Reactions	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	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%)

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

296 ^b Not approved for use in patients undergoing hip fracture surgery.

297 ^c Localized blister coded as bullous eruption.

298
 299 Adverse reactions in the abdominal surgery study and in the VTE treatment trials
 300 generally occurred at lower rates than in the hip and knee surgery trials described above. The
 301 most common adverse reaction in the abdominal surgery trial was post-operative wound
 302 infection (4.9%), and the most common adverse reaction in the VTE treatment trials was
 303 epistaxis (1.3%).

304 **6.5 Postmarketing Experience**

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

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

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

316 **7 DRUG INTERACTIONS**

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

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

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

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

333 **8 USE IN SPECIFIC POPULATIONS**

334 **8.1 Pregnancy**

335 Pregnancy Category B. Reproduction studies have been performed in pregnant rats at
336 subcutaneous doses up to 10 mg/kg/day (about 32 times the recommended human dose based on
337 body surface area) and pregnant rabbits at subcutaneous doses up to 10 mg/kg/day (about
338 65 times the recommended human dose based on body surface area) and have revealed no
339 evidence of impaired fertility or harm to the fetus due to fondaparinux sodium. There are,
340 however, no adequate and well-controlled studies in pregnant women. Because animal
341 reproduction studies are not always predictive of human response, ARIXTRA should be used
342 during pregnancy only if clearly needed.

343 **8.3 Nursing Mothers**

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

347 **8.4 Pediatric Use**

348 Safety and effectiveness of ARIXTRA in pediatric patients have not been established.
349 Because risk for bleeding during treatment with ARIXTRA is increased in adults who weigh
350 <50 kg, bleeding may be a particular safety concern for use of ARIXTRA in the pediatric
351 population [see *Warnings and Precautions (5.3)*].

352 **8.5 Geriatric Use**

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

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

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

367

368 **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)

369 ^a Includes hip fracture, hip replacement, and knee replacement surgery prophylaxis.

370

371 **8.6 Renal Impairment**

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

375 in patients who develop severe renal impairment while on therapy. After discontinuation of
376 ARIXTRA, its anticoagulant effects may persist for 2 to 4 days in patients with normal renal
377 function (i.e., at least 3 to 5 half-lives). The anticoagulant effects of ARIXTRA may persist even
378 longer in patients with renal impairment [see *Clinical Pharmacology (12.4)*].

379 **8.7 Hepatic Impairment**

380 Following a single, subcutaneous dose of 7.5 mg of ARIXTRA in patients with moderate
381 hepatic impairment (Child-Pugh Category B) compared to subjects with normal liver function,
382 changes from baseline in aPTT, PT/INR, and antithrombin III were similar in the two groups.
383 However, a higher incidence of hemorrhage was observed in subjects with moderate hepatic
384 impairment than in normal subjects, especially mild hematomas at the blood sampling or
385 injection site. The pharmacokinetics of fondaparinux have not been studied in patients with
386 severe hepatic impairment. [See *Dosage and Administration (2.4)* and *Clinical Pharmacology*
387 *(12.4)*.]

388 **10 OVERDOSAGE**

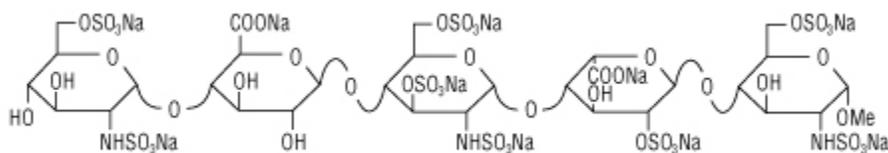
389 There is no known antidote for ARIXTRA. Overdose of ARIXTRA may lead to
390 hemorrhagic complications. Discontinue treatment and initiate appropriate therapy if bleeding
391 complications associated with overdose occur.

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

394 **11 DESCRIPTION**

395 ARIXTRA (fondaparinux sodium) Injection is a sterile solution containing fondaparinux
396 sodium. It is a synthetic and specific inhibitor of activated Factor X (Xa). Fondaparinux sodium
397 is methyl O-2-deoxy-6-O-sulfo-2-(sulfoamino)- α -D-glucopyranosyl-(1 \rightarrow 4)-O- β -D-glucopyra-
398 nuronosyl-(1 \rightarrow 4)-O-2-deoxy-3,6-di-O-sulfo-2-(sulfoamino)- α -D-glucopyranosyl-(1 \rightarrow 4)-O-2-O-
399 sulfo- α -L-idopyranuronosyl-(1 \rightarrow 4)-2-deoxy-6-O-sulfo-2-(sulfoamino)- α -D-glucopyranoside,
400 decasodium salt.

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



403
404 ARIXTRA is supplied as a sterile, preservative-free injectable solution for subcutaneous
405 use.

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

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

411 **12 CLINICAL PHARMACOLOGY**

412 **12.1 Mechanism of Action**

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

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

421 **12.2 Pharmacodynamics**

422 Anti-Xa Activity: The pharmacodynamics/pharmacokinetics of fondaparinux sodium are
423 derived from fondaparinux plasma concentrations quantified via anti-Factor Xa activity. Only
424 fondaparinux can be used to calibrate the anti-Xa assay. (The international standards of heparin
425 or LMWH are not appropriate for this use.) As a result, the activity of fondaparinux sodium is
426 expressed as milligrams (mg) of the fondaparinux calibrator. The anti-Xa activity of the drug
427 increases with increasing drug concentration, reaching maximum values in approximately
428 three hours.

429 **12.3 Pharmacokinetics**

430 Absorption: Fondaparinux sodium administered by subcutaneous injection is rapidly and
431 completely absorbed (absolute bioavailability is 100%). Following a single subcutaneous dose of
432 fondaparinux sodium 2.5 mg in young male subjects, C_{max} of 0.34 mg/L is reached in
433 approximately 2 hours. In patients undergoing treatment with fondaparinux sodium injection
434 2.5 mg, once daily, the peak steady-state plasma concentration is, on average, 0.39 to 0.50 mg/L
435 and is reached approximately 3 hours post-dose. In these patients, the minimum steady-state
436 plasma concentration is 0.14 to 0.19 mg/L. In patients with symptomatic deep vein thrombosis
437 and pulmonary embolism undergoing treatment with fondaparinux sodium injection 5 mg (body
438 weight <50 kg), 7.5 mg (body weight 50 to 100 kg), and 10 mg (body weight >100 kg) once
439 daily, the body-weight-adjusted doses provide similar mean steady-state peaks and minimum
440 plasma concentrations across all body weight categories. The mean peak steady-state plasma
441 concentration is in the range of 1.20 to 1.26 mg/L. In these patients, the mean minimum steady-
442 state plasma concentration is in the range of 0.46 to 0.62 mg/L.

443 Distribution: In healthy adults, intravenously or subcutaneously administered
444 fondaparinux sodium distributes mainly in blood and only to a minor extent in extravascular
445 fluid as evidenced by steady state and non-steady state apparent volume of distribution of 7 to
446 11 L. Similar fondaparinux distribution occurs in patients undergoing elective hip surgery or hip
447 fracture surgery. *In vitro*, fondaparinux sodium is highly (at least 94%) and specifically bound to

448 antithrombin III (ATIII) and does not bind significantly to other plasma proteins (including
449 platelet Factor 4 [PF4]) or red blood cells.

450 **Metabolism:** *In vivo* metabolism of fondaparinux has not been investigated since the
451 majority of the administered dose is eliminated unchanged in urine in individuals with normal
452 kidney function.

453 **Elimination:** In individuals with normal kidney function, fondaparinux is eliminated in
454 urine mainly as unchanged drug. In healthy individuals up to 75 years of age, up to 77% of a
455 single subcutaneous or intravenous fondaparinux dose is eliminated in urine as unchanged drug
456 in 72 hours. The elimination half-life is 17 to 21 hours.

457 **12.4 Special Populations**

458 **Renal Impairment:** Fondaparinux elimination is prolonged in patients with renal
459 impairment since the major route of elimination is urinary excretion of unchanged drug. In
460 patients undergoing prophylaxis following elective hip surgery or hip fracture surgery, the total
461 clearance of fondaparinux is approximately 25% lower in patients with mild renal impairment
462 (CrCl 50 to 80 mL/min), approximately 40% lower in patients with moderate renal impairment
463 (CrCl 30 to 50 mL/min), and approximately 55% lower in patients with severe renal impairment
464 (<30 mL/min) compared to patients with normal renal function. A similar relationship between
465 fondaparinux clearance and extent of renal impairment was observed in DVT treatment patients.
466 [*See Contraindications (4) and Warnings and Precautions (5.2).*]

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

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

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

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

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

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

494 **13 NONCLINICAL TOXICOLOGY**

495 **13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

496 No long-term studies in animals have been performed to evaluate the carcinogenic
497 potential of fondaparinux sodium.

498 Fondaparinux sodium was not genotoxic in the Ames test, the mouse lymphoma cell
499 (L5178Y/TK^{+/+}) forward mutation test, the human lymphocyte chromosome aberration test, the
500 rat hepatocyte unscheduled DNA synthesis (UDS) test, or the rat micronucleus test.

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

504 **14 CLINICAL STUDIES**

505 **14.1 Prophylaxis of Thromboembolic Events Following Hip Fracture Surgery**

506 In a randomized, double-blind, clinical trial in patients undergoing hip fracture surgery,
507 ARIXTRA 2.5 mg SC once daily was compared to enoxaparin sodium 40 mg SC once daily,
508 which is not approved for use in patients undergoing hip fracture surgery. A total of 1,711
509 patients were randomized and 1,673 were treated. Patients ranged in age from 17 to 101 years
510 (mean age 77 years) with 25% men and 75% women. Patients were 99% Caucasian, 1% other
511 races. Patients with multiple traumas affecting more than one organ system, serum creatinine
512 level more than 2 mg/dL (180 micromol/L), or platelet count less than 100,000/mm³ were
513 excluded from the trial. ARIXTRA was initiated after surgery in 88% of patients (mean 6 hours)
514 and enoxaparin sodium was initiated after surgery in 74% of patients (mean 18 hours). For both
515 drugs, treatment was continued for 7 ± 2 days. The primary efficacy endpoint, venous
516 thromboembolism (VTE), was a composite of documented deep vein thrombosis (DVT) and/or
517 documented symptomatic pulmonary embolism (PE) reported up to Day 11. The efficacy data
518 are provided in Table 7 and demonstrate that under the conditions of the trial ARIXTRA was
519 associated with a VTE rate of 8.3% compared with a VTE rate of 19.1% for enoxaparin sodium
520 for a relative risk reduction of 56% (95% CI: 39%, 70%; *P* <0.001). Major bleeding episodes
521 occurred in 2.2% of patients receiving ARIXTRA and 2.3% of enoxaparin sodium patients [*see*
522 *Adverse Reactions (6.1)*].

523

524 **Table 7. Efficacy of ARIXTRA in the Peri-operative Prophylaxis of Thromboembolic**
 525 **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)

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

529 ^b P value versus enoxaparin sodium <0.001.

530 ^c P value versus enoxaparin sodium: NS.

531

532 **14.2 Extended Prophylaxis of Thromboembolic Events Following Hip Fracture**
 533 **Surgery**

534 In a noncomparative, unblinded manner, 737 patients undergoing hip fracture surgery
 535 were initially treated during the peri-operative period with ARIXTRA 2.5 mg once daily for
 536 7 ± 1 days. Eighty-one (81) of the 737 patients were not eligible for randomization into the
 537 3-week double-blind period. Three hundred twenty-six (326) patients and 330 patients were
 538 randomized to receive ARIXTRA 2.5 mg once daily or placebo, respectively, in or out of the
 539 hospital for 21 ± 2 days. Patients ranged in age from 23 to 96 years (mean age 75 years) and
 540 were 29% men and 71% women. Patients were 99% Caucasian and 1% other races. Patients with
 541 multiple traumas affecting more than one organ system or serum creatinine level more than
 542 2 mg/dL (180 micromol/L) were excluded from the trial. The primary efficacy endpoint, venous
 543 thromboembolism (VTE), was a composite of documented deep vein thrombosis (DVT) and/or
 544 documented symptomatic pulmonary embolism (PE) reported for up to 24 days following
 545 randomization. The efficacy data are provided in Table 8 and demonstrate that extended
 546 prophylaxis with ARIXTRA was associated with a VTE rate of 1.4% compared with a VTE rate
 547 of 35.0% for placebo for a relative risk reduction of 95.9% (95% CI = [98.7; 87.1], P <0.0001).
 548 Major bleeding rates during the 3-week extended prophylaxis period for ARIXTRA occurred in
 549 2.4% of patients receiving ARIXTRA and 0.6% of placebo-treated patients [*see Adverse*
 550 *Reactions (6.1)*].
 551

552 **Table 8. Efficacy of ARIXTRA Injection in the Extended Prophylaxis of Thromboembolic**
 553 **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)

554 ^a N = all randomized evaluable hip fracture surgery patients. Evaluable patients were those who
 555 were treated in the post-randomization period, with an adequate efficacy assessment for up to
 556 24 days following randomization.

557 ^b P value versus placebo <0.001

558 ^c P value versus placebo = 0.021.

559 ^d P value versus placebo = NS.

560

561 **14.3 Prophylaxis of Thromboembolic Events Following Hip Replacement** 562 **Surgery**

563 In 2 randomized, double-blind, clinical trials in patients undergoing hip replacement
 564 surgery, ARIXTRA 2.5 mg SC once daily was compared to either enoxaparin sodium 30 mg SC
 565 every 12 hours (Study 1) or to enoxaparin sodium 40 mg SC once a day (Study 2). In Study 1, a
 566 total of 2,275 patients were randomized and 2,257 were treated. Patients ranged in age from 18
 567 to 92 years (mean age 65 years) with 48% men and 52% women. Patients were 94% Caucasian,
 568 4% black, <1% Asian, and 2% others. In Study 2, a total of 2,309 patients were randomized and
 569 2,273 were treated. Patients ranged in age from 24 to 97 years (mean age 65 years) with 42%
 570 men and 58% women. Patients were 99% Caucasian, and 1% other races. Patients with serum
 571 creatinine level more than 2 mg/dL (180 micromol/L), or platelet count less than 100,000/mm³
 572 were excluded from both trials. In Study 1, ARIXTRA was initiated 6 ± 2 hours (mean
 573 6.5 hours) after surgery in 92% of patients and enoxaparin sodium was initiated 12 to 24 hours
 574 (mean 20.25 hours) after surgery in 97% of patients. In Study 2, ARIXTRA was initiated 6 ± 2
 575 hours (mean 6.25 hours) after surgery in 86% of patients and enoxaparin sodium was initiated
 576 12 hours before surgery in 78% of patients. The first post-operative enoxaparin sodium dose was
 577 given within 12 hours after surgery in 60% of patients and 12 to 24 hours after surgery in 35% of
 578 patients with a mean of 13 hours. For both studies, both study treatments were continued for
 579 7 ± 2 days. The efficacy data are provided in Table 9. Under the conditions of Study 1,
 580 ARIXTRA was associated with a VTE rate of 6.1% compared with a VTE rate of 8.3% for
 581 enoxaparin sodium for a relative risk reduction of 26% (95% CI: -11%, 53%; P = NS). Under the

582 conditions of Study 2, fondaparinux sodium was associated with a VTE rate of 4.1% compared
 583 with a VTE rate of 9.2% for enoxaparin sodium for a relative risk reduction of 56% (95% CI:
 584 33%, 73%; $P < 0.001$). For the 2 studies combined, the major bleeding episodes occurred in 3.0%
 585 of patients receiving ARIXTRA and 2.1% of enoxaparin sodium patients [see Adverse Reactions
 586 (6.1)].

587

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

Endpoint	Study 1 n/N ^a % (95% CI)		Study 2 n/N ^a % (95% CI)	
	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)

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

593 ^b VTE was a composite of documented DVT and/or documented symptomatic PE reported up
 594 to Day 11.

595 ^c P value versus enoxaparin sodium: NS.

596 ^d P value versus enoxaparin sodium in study 1: < 0.05 .

597 ^e P value versus enoxaparin sodium in study 2: < 0.001 .

598 ^f P value versus enoxaparin sodium in study 2: < 0.01 .

599

600 **14.4 Prophylaxis of Thromboembolic Events Following Knee Replacement** 601 **Surgery**

602 In a randomized, double-blind, clinical trial in patients undergoing knee replacement
 603 surgery (i.e., surgery requiring resection of the distal end of the femur or proximal end of the
 604 tibia), ARIXTRA 2.5 mg SC once daily was compared to enoxaparin sodium 30 mg SC every
 605 12 hours. A total of 1,049 patients were randomized and 1,034 were treated. Patients ranged in
 606 age from 19 to 94 years (mean age 68 years) with 41% men and 59% women. Patients were 88%

607 Caucasian, 8% black, <1% Asian, and 3% others. Patients with serum creatinine level more than
 608 2 mg/dL (180 micromol/L), or platelet count less than 100,000/mm³ were excluded from the
 609 trial. ARIXTRA was initiated 6 ± 2 hours (mean 6.25 hours) after surgery in 94% of patients,
 610 and enoxaparin sodium was initiated 12 to 24 hours (mean 21 hours) after surgery in 96% of
 611 patients. For both drugs, treatment was continued for 7 ± 2 days. The efficacy data are provided
 612 in Table 10 and demonstrate that under the conditions of the trial, ARIXTRA was associated
 613 with a VTE rate of 12.5% compared with a VTE rate of 27.8% for enoxaparin sodium for a
 614 relative risk reduction of 55% (95% CI: 36%, 70%; *P* <0.001). Major bleeding episodes occurred
 615 in 2.1% of patients receiving ARIXTRA and 0.2% of enoxaparin sodium patients [*see Adverse*
 616 *Reactions (6.1)*].

617
 618 **Table 10. Efficacy of ARIXTRA in the Prophylaxis of Thromboembolic Events Following**
 619 **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)

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

623 ^b VTE was a composite of documented DVT and/or documented symptomatic PE reported up
 624 to Day 11.

625 ^c *P* value versus enoxaparin sodium <0.001.

626 ^d *P* value versus enoxaparin sodium: NS.

627

628 **14.5 Prophylaxis of Thromboembolic Events Following Abdominal Surgery in** 629 **Patients at Risk for Thromboembolic Complications**

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

637 In a randomized, double-blind, clinical trial in patients undergoing abdominal surgery,
 638 ARIXTRA 2.5 mg SC once daily started postoperatively was compared to dalteparin sodium
 639 5,000 IU SC once daily, with one 2,500 IU SC preoperative injection and a 2,500 IU SC first

640 postoperative injection. A total of 2,927 patients were randomized and 2,858 were treated.
 641 Patients ranged in age from 17 to 93 years (mean age 65 years) with 55% men and 45% women.
 642 Patients were 97% Caucasian, 1% black, 1% Asian, and 1% others. Patients with serum
 643 creatinine level more than 2 mg/dL (180 micromol/L), or platelet count less than 100,000/mm³
 644 were excluded from the trial. Sixty-nine percent (69%) of study patients underwent cancer-
 645 related abdominal surgery. Study treatment was continued for 7 ± 2 days. The efficacy data are
 646 provided in Table 11 and demonstrate that prophylaxis with ARIXTRA was associated with a
 647 VTE rate of 4.6% compared with a VTE rate of 6.1% for dalteparin sodium (*P* = NS).
 648

649 **Table 11. Efficacy of ARIXTRA In Prophylaxis of Thromboembolic Events Following**
 650 **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)

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

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

656 ^c *P* value versus dalteparin sodium: NS.
 657

658 **14.6 Treatment of Deep Vein Thrombosis**

659 In a randomized, double-blind, clinical trial in patients with a confirmed diagnosis of
 660 acute symptomatic DVT without PE, ARIXTRA 5 mg (body weight <50 kg), 7.5 mg (body
 661 weight 50 to 100 kg), or 10 mg (body weight >100 kg) SC once daily (ARIXTRA treatment
 662 regimen) was compared to enoxaparin sodium 1 mg/kg SC every 12 hours. Almost all patients
 663 started study treatment in hospital. Approximately 30% of patients in both groups were
 664 discharged home from the hospital while receiving study treatment. A total of 2,205 patients
 665 were randomized and 2,192 were treated. Patients ranged in age from 18 to 95 years (mean age
 666 61 years) with 53% men and 47% women. Patients were 97% Caucasian, 2% black, and 1%
 667 other races. Patients with serum creatinine level more than 2 mg/dL (180 micromol/L), or
 668 platelet count less than 100,000/mm³ were excluded from the trial. For both groups, treatment
 669 continued for at least 5 days with a treatment duration range of 7 ± 2 days, and both treatment
 670 groups received vitamin K antagonist therapy initiated within 72 hours after the first study drug
 671 administration and continued for 90 ± 7 days, with regular dose adjustments to achieve an INR

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

674

675 **Table 12. Efficacy of ARIXTRA in the Treatment of Deep Vein Thrombosis (All**
 676 **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)

677 ^a VTE was a composite of symptomatic recurrent non-fatal VTE or fatal PE reported up to Day
 678 97. The 95% confidence interval for the treatment difference for total VTE was: (-1.8% to
 679 1.5%).

680

681 During the initial treatment period, 18 (1.6%) of patients treated with fondaparinux
 682 sodium and 10 (0.9%) of patients treated with enoxaparin sodium had a VTE endpoint (95% CI
 683 for the treatment difference [fondaparinux sodium-enoxaparin sodium] for VTE rates: -0.2%;
 684 1.7%).

685 **14.7 Treatment of Pulmonary Embolism**

686 In a randomized, open-label, clinical trial in patients with a confirmed diagnosis of acute
 687 symptomatic PE, with or without DVT, ARIXTRA 5 mg (body weight <50 kg), 7.5 mg (body
 688 weight 50 to 100 kg), or 10 mg (body weight >100 kg) SC once daily (ARIXTRA treatment
 689 regimen) was compared to heparin IV bolus (5,000 USP units) followed by a continuous IV
 690 infusion adjusted to maintain 1.5 to 2.5 times aPTT control value. Patients with a PE requiring
 691 thrombolysis or surgical thrombectomy were excluded from the trial. All patients started study
 692 treatment in hospital. Approximately 15% of patients were discharged home from the hospital
 693 while receiving ARIXTRA therapy. A total of 2,213 patients were randomized and 2,184 were
 694 treated. Patients ranged in age from 18 to 97 years (mean age 62 years) with 44% men and 56%
 695 women. Patients were 94% Caucasian, 5% black, and 1% other races. Patients with serum
 696 creatinine level more than 2 mg/dL (180 micromol/L), or platelet count less than 100,000/mm³
 697 were excluded from the trial. For both groups, treatment continued for at least 5 days with a
 698 treatment duration range 7 ± 2 days, and both treatment groups received vitamin K antagonist
 699 therapy initiated within 72 hours after the first study drug administration and continued for
 700 90 ± 7 days, with regular dose adjustments to achieve an INR of 2 to 3. The primary efficacy
 701 endpoint was confirmed, symptomatic, recurrent VTE reported up to Day 97. The efficacy data
 702 are provided in Table 13.

703

704 **Table 13. Efficacy of ARIXTRA in the Treatment of Pulmonary Embolism (All**
 705 **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)

706 ^a VTE was a composite of symptomatic recurrent non-fatal VTE or fatal PE reported up to
 707 Day 97. The 95% confidence interval for the treatment difference for total VTE was:
 708 (-3.0% to 0.5%).
 709

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

713 **16 HOW SUPPLIED/STORAGE AND HANDLING**

714 ARIXTRA Injection is available in the following strengths and package sizes:
 715 2.5 mg ARIXTRA in 0.5 mL single-dose prefilled syringe, affixed with a 27-gauge x
 716 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
 717 5 mg ARIXTRA in 0.4 mL single-dose prefilled syringe, affixed with a 27-gauge x
 718 ½-inch needle and an automatic needle protection system with white plunger rod.
 NDC 0007-3232-02 2 Single Unit Syringes
 NDC 0007-3232-11 10 Single Unit Syringes
 719 7.5 mg ARIXTRA in 0.6 mL single-dose prefilled syringe, affixed with a 27-gauge x
 720 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
 721 10 mg ARIXTRA in 0.8 mL single-dose prefilled syringe, affixed with a 27-gauge x
 722 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
 723 Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F).

724 **17 PATIENT COUNSELING INFORMATION**

725 *See FDA-Approved Patient Labeling (17.2)*

726 **17.1 Patient Advice**

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

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

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

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

751 **Keep out of the reach of children.**

752 **17.2 FDA-Approved Patient Labeling**

753 Patient labeling is provided as a tear-off leaflet at the end of this full prescribing information.
754

755 ARIXTRA is a registered trademark of GlaxoSmithKline.
756



757
758 GlaxoSmithKline
759 Research Triangle Park, NC 27709
760

761 ©YEAR, GlaxoSmithKline. All rights reserved.

762

763 ARX:XPI

764 **PHARMACIST-DETACH HERE AND GIVE INSTRUCTIONS TO PATIENT**



766
767 **PATIENT INFORMATION**
768 **ARIXTRA® (Ah-RIX-trah)**
769 **fondaparinux sodium injection**
770

771 Read the Patient Information that comes with ARIXTRA before you start taking it
772 and each time you get a refill. There may be new information. This information
773 does not take the place of talking with your doctor about your medical condition or
774 your treatment. If you have any questions about ARIXTRA, ask your doctor or
775 pharmacist.
776

777 **What is the most important information I should know about ARIXTRA?**

778 Certain medical procedures involving the spine, such as an epidural (pain
779 medication given through the spine), spinal anesthesia, or spinal puncture, may be
780 used during your hospital stay. If you need any of these procedures while receiving
781 ARIXTRA, heparins, heparinoids, or low-molecular weight heparins (anticoagulants),
782 you may be at risk for having a blood clot (hematoma) in or around your spine.
783 This type of clot is very serious, as it can cause long-term and possibly permanent
784 paralysis (loss of the ability to move).
785

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

- 790 • tingling
 - 791 • numbness
 - 792 • muscle weakness
- 793

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

- 796 • are also taking certain other medicines that affect blood clotting such as aspirin,
797 an NSAID (for example, ibuprofen or naproxen), clopidogrel, or warfarin sodium.
 - 798 • have bleeding problems.
 - 799 • had problems in the past with pain medication given through the spine.
 - 800 • have had surgery to your spine.
 - 801 • have a spinal deformity.
- 802

803 **What is ARIXTRA?**

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

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

810
811 It is not known if ARIXTRA is safe and effective for use in children younger than 18
812 years of age.

813
814 **Who should not take ARIXTRA?**

815 Do not take ARIXTRA if you have:

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

822
823 People who weigh less than 110 pounds (50 kg) should not use ARIXTRA to prevent
824 blood clots from forming after surgery.

825
826 **What should I tell my doctor before taking ARIXTRA?**

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

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

840

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

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

847

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

850

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

855

856 **How should I take ARIXTRA?**

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

871

872 **What are possible side effects of ARIXTRA?**

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

875

- 876 • Severe **bleeding**
 - 877 • Certain conditions can increase your risk for severe bleeding, including:
878 -some bleeding problems
879 -some gastrointestinal problems including ulcers
880 -some types of strokes

881 -uncontrolled high blood pressure
882 -diabetic eye disease
883 -soon after brain, spine, or eye surgery
884 • **Certain kidney problems can also increase your risk of bleeding with**
885 **ARIXTRA.** Your doctor may check your kidney function while you are taking
886 ARIXTRA.
887 • **People undergoing surgery who weigh less than 110 pounds.** See
888 “Who should not take ARIXTRA?”
889 • **Low blood platelets.** Low blood platelets can happen when you take
890 ARIXTRA. Platelets are blood cells that help your blood to clot normally. Your
891 doctor may check your platelet counts while you take ARIXTRA.
892 You may bruise or bleed more easily while taking ARIXTRA, and it may take
893 longer than usual for bleeding to stop.
894 Tell your doctor if you have any of these signs or symptoms of bleeding while
895 taking ARIXTRA.
896 -any bleeding
897 -bruising
898 -rash of dark red spots under the skin
899 • **Allergic reactions (itching, swelling, or rash).** See “What should I tell my
900 doctor before taking ARIXTRA?” Serious allergic reactions can happen when you
901 take ARIXTRA. If you experience swelling of the face or mouth or have difficulty
902 in swallowing or breathing, contact your doctor right away. You should stop
903 ARIXTRA if this happens.
904
905 Other side effects include:
906 • **Injection site reactions.** Bleeding, rash, and itching can happen at the place
907 where you inject ARIXTRA.
908 • **Low red blood cell counts (anemia).** Your doctor may check your red blood
909 cell counts while you are taking ARIXTRA.
910 • **Increased liver enzyme test results.** Your doctor may check your liver
911 function while you are taking ARIXTRA.
912 • **Sleep problems (insomnia).**
913
914 These are not all the possible side effects of ARIXTRA. Call your doctor if you have
915 any side effects that bother you or don’t go away.
916
917 Call your doctor for medical advice about side effects. You may report side effects
918 to the FDA at 1-800-FDA-1088.
919

920 **How should I store ARIXTRA?**

921 Store ARIXTRA at room temperature 59°F to 86°F (15°C to 30°C). Do not freeze.
922 Safely, throw away ARIXTRA that is out of date or no longer needed.

923 **Keep ARIXTRA and all medicines out of the reach of children.**

924

925 **General information about ARIXTRA**

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

929

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

935

936 **What are the ingredients in ARIXTRA?**

937 Active Ingredient: fondaparinux sodium

938 Inactive Ingredients: sodium chloride and water for injection

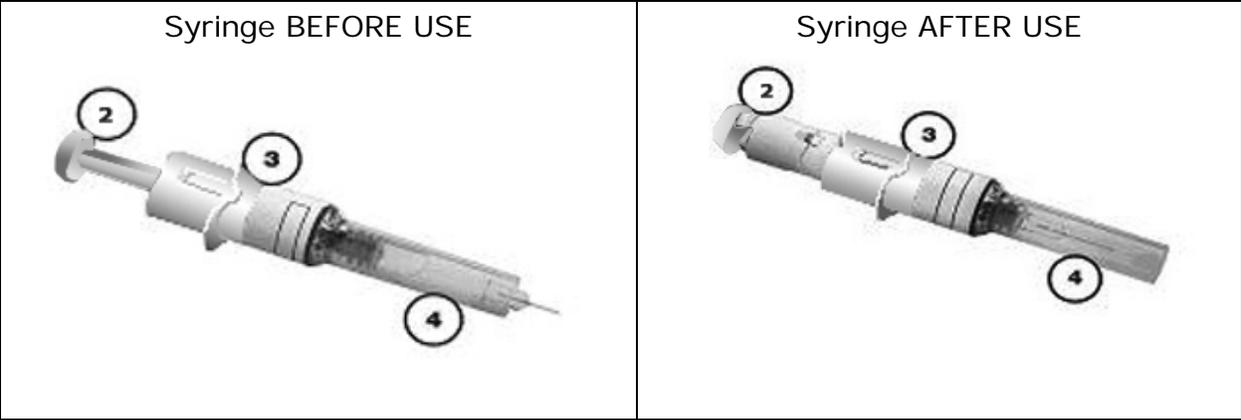
939

940 **How should I give an injection of ARIXTRA?**

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

946

<u>Instructions for self-administration</u>	
The different parts of ARIXTRA safety syringe are:	
<ol style="list-style-type: none">1. Rigid needle guard2. Plunger3. Finger-grip4. Security sleeve	



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.

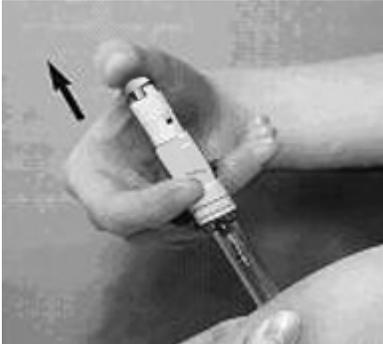
3. Clean the injection area with an alcohol swab.

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.

<p>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).</p>		<p>Figure C.</p>
<p>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).</p>		<p>Figure D.</p>
<p>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).</p>		<p>Figure E.</p>
<p>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).</p>		<p>Figure F.</p>
<p>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.</p>		

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