



SB 486 Safe Needle Disposal Plan for 2014 – 2015

Submitted to:

**Department of Resources Recycling and Recovery
(CalRecycle)**

1 July 2015

Background

The State of California has enacted two laws to address home generated sharps disposal. The first law (SB 1305), makes it illegal for any person in the state of California to dispose of home generated sharps waste in the trash or recycling containers, and requires that all sharps waste be transported to a collection center in an approved sharps container. This law became effective September 1, 2008. In 2009, California enacted (SB 486) which requires any pharmaceutical manufacturer that sells or distributes medication that is self-injected at home through the use of hypodermic needles and other similar devices to submit to the board, or its successor agency, a plan that describes how the manufacturer supports the safe collection and proper disposal of waste devices. This plan is due on July 1, 2010 and annually thereafter.

Dr. Reddy's Laboratories, Inc. Self-Injectable Products

Subject To These Regulations In California

Dr. Reddy's Laboratories, Inc. currently markets, distributes, and/or sells two self-injectable products in the State of California. The generic names of these products are fondaparinux sodium injection (subcutaneous) and sumatriptan injection (subcutaneous).

Dr. Reddy's Laboratories, Inc. Supports Safe Collection

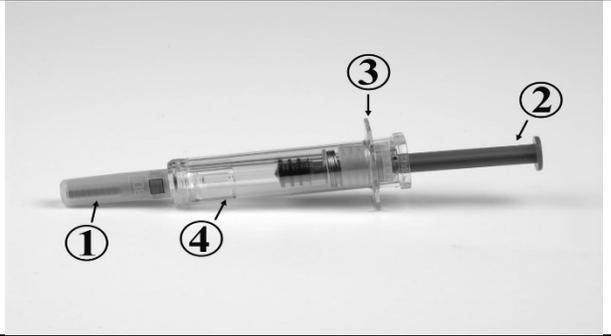
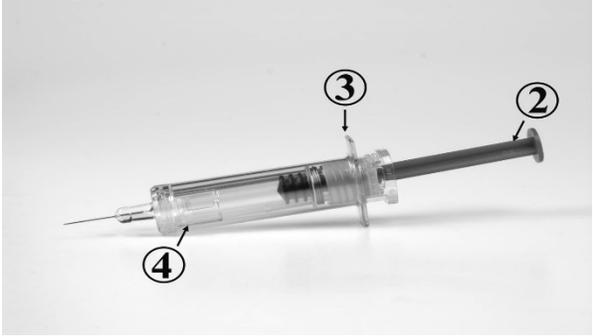
and Proper Disposal of Home Generated Sharps

Dr. Reddy's Laboratories, Inc. supports appropriate and safe disposal of home-generated waste sharps. Patient safety and needle stick injury prevention were given serious consideration as the above-mentioned products were being developed.

Fondaparinux

During the development of fondaparinux sodium injection (subcutaneous), Dr. Reddy's Laboratories, Inc. employed safe needle technology in order to protect patients and those assisting in the disposal of waste sharps. Specifically, fondaparinux sodium injection uses a 27 gauge needle that is only a half-inch long and an automatic needle protection system covers the needle after the injection. The steps to activate the automatic needle protection system are described in the fondaparinux sodium injection (subcutaneous) Patient Information Leaflet.

Automatic Needle Protection System:

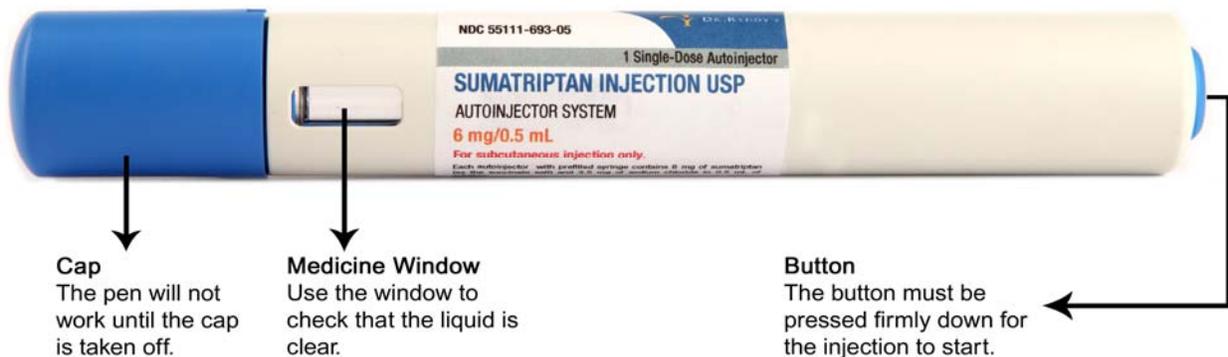
<p>The different parts of fondaparinux sodium safety syringe are:</p>	
<ol style="list-style-type: none">1. Rigid Needle Shield2. Plunger3. Finger-grip4. Safety shield	
<p>Syringe BEFORE USE</p> 	<p>Syringe AFTER USE</p> 

Sumatriptan

Sumatriptan injection autoinjector system is available for use with a 6 mg prefilled syringe to facilitate self-administration in patients using the 6 mg dose. With this device, the needle penetrates approximately ¼ inch (5 to 6 mm). The steps to activate the autoinjector system are described in the sumatriptan injection (subcutaneous) Patient Information and Instructions for Use.

About the Autoinjector Pen

The parts of the pen are shown in this picture.



Patient Education Materials:

Patients who self-inject Dr. Reddy's Laboratories, Inc. products at home should receive instructions from their healthcare professionals on how to use these products properly. The full prescribing information is available to healthcare professionals. Patients should read the Patient Information Leaflet that comes with each product before they start taking each product and each time the prescription is refilled as there may be new information.

Dr. Reddy's Laboratories, Inc. has also created a patient specific website for sumatriptan injection (subcutaneous) at www.drreddys.com/products/NA/sumatriptan.html . This website provides patients with the most important information they need to know from Dr. Reddy's Laboratories. The information on this website does not take the place of talking with the patient's doctor about the medical conditions or treatments. Patients can view sumatriptan self-administration instructions in English in text or as a video.

Patients and caregivers can also contact a Dr. Reddy's Laboratories, Inc. representative at 1-888-375-3784. Pharmacists are available Monday through Friday 8:00 am to 10:00 pm ET to assist with questions about these products.

Disposal:

Patients and consumers have several options available to them to safely dispose sharps waste.

Patients may visit California's CalRecycle website at <http://www.calrecycle.ca.gov/HomeHazWaste/Sharps/Household.htm> to become familiar with all disposal options available and select the option that is most convenient. Below are disposal options detailed on the California CalRecycle website:

- Patients may use the [Disposal Directory \(FacIT\) for Sharps and Medication](#) (via link <http://www.calrecycle.ca.gov/facit/facility/search.aspx>). In this directory, you may locate facilities that collect sharps for disposal near to where you live or work. Collection programs include:
 - **Pharmacies.** Some drug stores take back their customers' needles, especially in small quantities.
 - **Hospitals.** Hospitals may take back sharps from patients using regular outpatient services.
 - **Local Household Hazardous Waste Programs.** Call your local household hazardous waste agency and ask if they collect needles (sharps) at their collection facilities or on household hazardous waste days. You can also look for this information here:
 - Your local white pages' government section may list your city's or county's household hazardous waste department.
 - Visit the [Earth 911.org](http://www.earth911.org) website or call 1-800-CLEANUP (1-800-253-2687), a service of Earth 911.
 - Visit the [Local Enforcement Agency Directory](#) on this website.
- [Local Jurisdiction Sharps Collection Programs.](#) A file showing a sampling of local jurisdictions' sharps collection programs and containing contacts, e-mail addresses, program summaries, and

outreach materials. This spreadsheet could help jurisdictions that don't currently have collection programs to set up their own sharps collection program.

- **Needle Destruction Devices.** The U.S. Food and Drug Administration (FDA) currently only lists the [“Disintegrator”](#) as a needle destruction device approved for use by self-injectors.
- **Mail-Back Service.** A list of sharps waste mail-back services authorized for use in California is available from the [California Department Of Public Health \(CDPH\)](#) (PDF, 90 KB).
- **Sharps Containers.** The California Department of Public Health Medical Waste Management Program is recommending the use of [sharps containers approved by the FDA](#). After accessing the FDA website, type “sharps” in the search box. The container names will display alphabetically.

For More Information

Stay informed about the latest developments in CalRecycle's efforts to promote safe disposal of sharps waste.

- **Listserv:** To receive periodic information about sharps, subscribe to the [Sharps and Medication Disposal Listserv](#).
- **Contact:** Please contact pharmasharps@calrecycle.ca.gov for questions or more information.

Company Contact Information:

If you would like assistance from Dr. Reddy's Laboratories, Inc. in identifying your disposal options, please contact a Dr. Reddy's Laboratories, Inc. representative at 1-888-375-3784. Representatives are available to assist patients with questions about each of these products, including product administration and medical waste disposal.

Dr. Reddy's Laboratories, Inc. remains committed to help facilitate the safe disposal of its products and will continue to evaluate feedback and make modifications to this plan as needed.

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

FONDAPARINUX sodium injection for subcutaneous use

Initial U.S. Approval: 2001

WARNING: SPINAL/EPIDURAL HEMATOMAS

See full prescribing information for complete boxed warning.

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

Boxed Warning	07/2014
Contraindications (4)	09/2013
Warnings and Precautions (5.5)	07/2014

INDICATIONS AND USAGE

Fondaparinux sodium injection 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: Fondaparinux sodium 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: Fondaparinux sodium 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

Fondaparinux sodium injection 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 fondaparinux sodium.

WARNINGS AND PRECAUTIONS

- Use with caution in patients who have conditions or who 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 fondaparinux sodium. (5.4)
- Periodic routine complete blood counts (including platelet counts), serum creatinine level, and stool occult blood tests are recommended (5.6)

ADVERSE REACTIONS

The most common adverse reactions associated with the use of fondaparinux sodium 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 Dr. Reddy's Laboratories, Inc. at 1-888-375-3784 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 fondaparinux sodium unless essential. If co-administration is necessary, monitor patients closely for hemorrhage. (7)

USE IN SPECIFIC POPULATIONS

- Safety and effectiveness of fondaparinux sodium in pediatric patients have not been established. Because the risk for bleeding during treatment with fondaparinux sodium is increased in adults who weigh <50 kg, bleeding may be a particular safety concern for use of fondaparinux sodium in the pediatric population. (4, 5.3)
- Because elderly patients are more likely to have reduced renal function, fondaparinux sodium 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: 09/2014

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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
- Optimal timing between the administration of fondaparinux sodium and neuraxial procedures is not known.

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

Fondaparinux sodium injection 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

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

1.3 Treatment of Acute Pulmonary Embolism

Fondaparinux sodium injection 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 fondaparinux sodium injection. Administer fondaparinux sodium injection 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 fondaparinux sodium injection 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 fondaparinux sodium injection 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 fondaparinux sodium injection 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 fondaparinux sodium injection 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 fondaparinux sodium injection 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 fondaparinux sodium injection 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 (fondaparinux sodium treatment regimen). Initiate concomitant treatment with warfarin sodium as soon as possible, usually within 72 hours. Continue treatment with fondaparinux sodium injection for at least 5 days and until a therapeutic oral anticoagulant effect is established (INR 2 to 3). The usual duration of administration of fondaparinux sodium injection is 5 to 9 days; up to 26 days of fondaparinux sodium 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 fondaparinux sodium therapy. Observe these patients closely for signs and symptoms of bleeding. [See **Clinical Pharmacology (12.4)**].

2.5 Instructions for Use

Fondaparinux sodium injection is provided in a single-dose, prefilled syringe affixed with an active needle protection system. Fondaparinux sodium is administered by subcutaneous injection. It must not be administered by intramuscular injection. Fondaparinux sodium injection 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 fondaparinux sodium injection to ensure the solution is clear and free of particulate matter. **The following instructions are specific to the Preventis™ injection system and may differ from the directions for other injection systems.**

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 fondaparinux sodium:

STEP 1:

- Wipe the surface of the injection site with an alcohol swab.
- Remove the needle shield by pulling it straight off the syringe (Figure 1).
- Discard the needle shield.

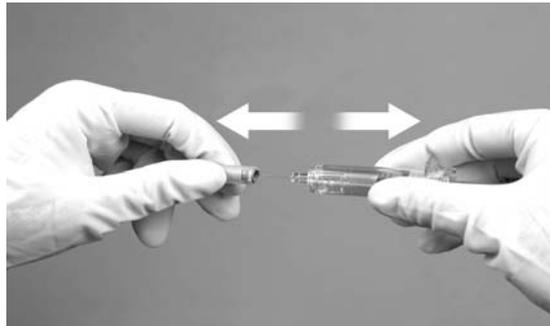


Figure 1

STEP 2:

- Do not try to remove the air bubbles from the syringe before giving the injection.
- Pinch a fold of skin at the injection site between your thumb and forefinger and hold it throughout the injection time.
- Hold the syringe with your thumb on the top pad of the plunger and keep your index and middle fingers on the finger-grips of the syringe barrel. Pay attention to avoid pricking yourself with the exposed needle.
- Insert the full length of the syringe needle perpendicularly into the skin fold held between the thumb and forefinger (Figure 2).
- Push the plunger to the bottom of the syringe. This will ensure you have injected all the contents of the syringe.



Figure 2

STEP 3:

- Remove the syringe from the injection site keeping your finger on the plunger (Figure 3).



Figure 3

STEP 4:

- Orient the needle away from you and others, and activate the safety shield by firmly pushing the plunger. The protective sleeve will automatically cover the needle and an audible "click" will be heard to confirm shield activation (Figure 4).



Figure 4

STEP 5:

- Immediately discard the syringe into the sharps container (Figure 5).



Figure 5

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

Fondaparinux sodium injection 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 fondaparinux sodium.

5 WARNINGS AND PRECAUTIONS

5.1 Hemorrhage

Use fondaparinux sodium 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 fondaparinux sodium (with or without concomitant administration of other anticoagulants) [See **Adverse Reactions (6.5)**].

Do not administer agents that enhance the risk of hemorrhage with fondaparinux sodium 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 fondaparinux sodium 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

Fondaparinux sodium 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 fondaparinux sodium for VTE surgical prophylaxis is provided in Table 1. In these patient populations, the following is recommended:

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

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

CrCl = creatinine clearance.

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

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

5.3 Body Weight <50 Kg and Bleeding Risk

Fondaparinux sodium 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 fondaparinux sodium as prophylactic therapy for patients undergoing hip fracture, hip replacement, or knee replacement surgery and abdominal surgery [see **Contraindications (4)**].
- Use fondaparinux sodium 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 fondaparinux sodium. Thrombocytopenia of any degree should be monitored closely. Discontinue fondaparinux sodium if the platelet count falls below 100,000/mm³. Moderate thrombocytopenia (platelet counts between 100,000/mm³ and 50,000/mm³) occurred at a rate of 3.0% in patients given fondaparinux sodium 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/mm³) occurred at a rate of 0.2% in patients given fondaparinux sodium 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 fondaparinux sodium treatment regimen in the DVT and PE treatment clinical trials. Severe thrombocytopenia occurred at a rate of 0.04% in patients given the fondaparinux sodium 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 fondaparinux sodium 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 fondaparinux sodium by subcutaneous (SC) injection. Optimal timing between the administration of fondaparinux sodium and neuraxial procedures is not known. Monitor patients undergoing these procedures for signs and symptoms of neurologic impairment such as midline back pain, sensory and motor deficits (numbness, tingling, or weakness in lower limbs), and bowel or bladder dysfunction. 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 fondaparinux sodium and international standards of heparin or LMWH are not calibrators to measure anti-Factor Xa activity of fondaparinux sodium. If unexpected changes in coagulation parameters or major bleeding occur during therapy with fondaparinux sodium, discontinue fondaparinux sodium. In postmarketing experience, isolated occurrences of aPTT elevations have been reported following administration of fondaparinux sodium [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 fondaparinux sodium.

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)**].

6 ADVERSE REACTIONS

The most serious adverse reactions reported with fondaparinux sodium 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 fondaparinux sodium 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 fondaparinux sodium, 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 fondaparinux sodium 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)	
	Fondaparinux Sodium 2.5 mg SC once daily N = 3,616	Enoxaparin Sodium ^{a, b} N = 3,956	Fondaparinux Sodium 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 fondaparinux sodium after surgical closure was performed in patients who received fondaparinux sodium 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, fondaparinux sodium 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

	Fondaparinux Sodium 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 fondaparinux sodium 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 fondaparinux sodium injection treatment regimen are provided in Table 4.

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

	Fondaparinux Sodium 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 fondaparinux sodium.

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 fondaparinux sodium 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 fondaparinux sodium 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 fondaparinux sodium. 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 fondaparinux sodium should be interpreted with caution.

6.4 Other Adverse Reactions

Other adverse reactions that occurred during treatment with fondaparinux sodium 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

Adverse Reactions	Peri-Operative Prophylaxis (Day 1 to Day 7 \pm 1 post-surgery)		Extended Prophylaxis (Day 8 to Day 28 \pm 2 post-surgery)	
	Fondaparinux Sodium 2.5 mg SC once daily	Enoxaparin Sodium ^{a,b}	Fondaparinux Sodium 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 fondaparinux sodium. 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.

In the postmarketing experience, epidural or spinal hematoma has been reported in association with the use of fondaparinux sodium by subcutaneous (SC) injection [see **Warnings and Precautions (5.5)**]. 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 fondaparinux sodium (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 fondaparinux sodium [see **Contraindications (4)**].

7 DRUG INTERACTIONS

In clinical studies performed with fondaparinux sodium, 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, fondaparinux sodium 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 fondaparinux sodium 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, fondaparinux sodium 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 fondaparinux sodium is administered to a nursing mother.

8.4 Pediatric Use

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

8.5 Geriatric Use

In clinical trials the efficacy of fondaparinux sodium 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 fondaparinux sodium 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 fondaparinux sodium 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 fondaparinux sodium 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 fondaparinux sodium 2.5 mg, serious adverse events increased with age for patients receiving fondaparinux sodium. The incidence of major bleeding in clinical trials of fondaparinux sodium by age is provided in Table 6.

Table 6. Incidence of Major Bleeding in Patients Treated With Fondaparinux Sodium 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 fondaparinux sodium [see **Contraindications (4) and Warnings and Precautions (5.2)**]. Assess renal function periodically in patients receiving fondaparinux sodium. Discontinue fondaparinux sodium immediately in patients who develop severe renal impairment while on therapy. After discontinuation of fondaparinux sodium, 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 fondaparinux sodium 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 fondaparinux sodium 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

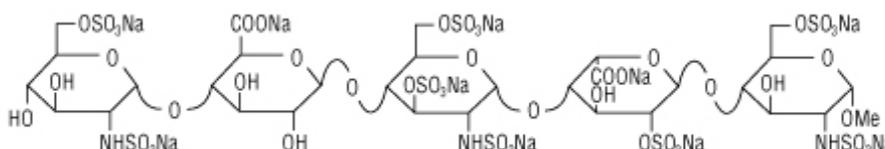
There is no known antidote for fondaparinux sodium. Overdose of fondaparinux sodium may lead to hemorrhagic complications. Discontinue treatment and initiate appropriate therapy if bleeding complications associated with overdose occur.

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

11 DESCRIPTION

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 \rightarrow 4)-O- β -D-glucopyranuronosyl-(1 \rightarrow 4)-O-2-deoxy-3,6-di-O-sulfo-2-(sulfoamino)- α -D-glucopyranosyl-(1 \rightarrow 4)-O-2-Osulfo- α -L-idopyranuronosyl-(1 \rightarrow 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:



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

Each single-dose, prefilled syringe of fondaparinux sodium, affixed with an active 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, water for injection. Also contain hydrochloric acid and sodium hydroxide as pH adjusters. The final drug product is a clear and colorless to slightly yellow liquid with a pH between 5.5 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 fondaparinux sodium 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, fondaparinux sodium 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/mm³ were excluded from the trial. Fondaparinux sodium 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 fondaparinux sodium 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 fondaparinux sodium and 2.3% of enoxaparin sodium patients [see **Adverse Reactions (6.1)**].

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

Endpoint	Peri-operative Prophylaxis (Day 1 to Day 7 ± 2 post-surgery)			
	Fondaparinux Sodium 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 fondaparinux sodium 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 fondaparinux sodium 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 fondaparinux sodium 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 fondaparinux sodium occurred in 2.4% of patients receiving fondaparinux sodium and 0.6% of placebo-treated patients [see **Adverse Reactions (6.1)**].

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

Endpoint	Extended Prophylaxis (Day 8 to Day 28 \pm 2 post-surgery)			
	Fondaparinux Sodium 2.5 mg SC once daily		Placebo SC once daily	
	n/N ^a	% (95% CI)	n/Na	% (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, fondaparinux sodium 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/mm³ were excluded from both trials. In Study 1, fondaparinux sodium 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, fondaparinux sodium 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, fondaparinux sodium 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%; $P = \text{NS}$). 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 fondaparinux sodium and 2.1% of enoxaparin sodium patients [see **Adverse Reactions (6.1)**].

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

Endpoint	Study 1 n/N ^a % (95% CI)		Study 2 n/N ^a % (95% CI)	
	Fondaparinux Sodium 2.5 mg SC once daily	Enoxaparin Sodium 30 mg SC every 12 hr	Fondaparinux Sodium 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), fondaparinux sodium 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 $100,000/\text{mm}^3$ were excluded

from the trial. Fondaparinux sodium 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, fondaparinux sodium 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 fondaparinux sodium and 0.2% of enoxaparin sodium patients [see **Adverse Reactions (6.1)**].

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

Endpoint	Fondaparinux Sodium 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)

^aN = 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.

^bVTE was a composite of documented DVT and/or documented symptomatic PE reported up to Day 11.

^cP value versus enoxaparin sodium < 0.001 .

^dP 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, fondaparinux sodium 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/mm³ 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 fondaparinux sodium was associated with a VTE rate of 4.6% compared with a VTE rate of 6.1% for dalteparin sodium ($P = \text{NS}$).

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

Endpoint	Fondaparinux Sodium 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, fondaparinux sodium 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 (fondaparinux sodium 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/mm³ 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 Fondaparinux Sodium in the Treatment of Deep Vein Thrombosis (All Randomized)

Endpoint	Fondaparinux Sodium 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, fondaparinux sodium 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 (fondaparinux sodium 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 fondaparinux sodium 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/mm³ 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 Fondaparinux Sodium in the Treatment of Pulmonary Embolism (All Randomized)

Endpoint	Fondaparinux Sodium 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

Fondaparinux sodium injection is available in the following strengths and package sizes:

2.5 mg fondaparinux sodium in 0.5 mL single dose prefilled syringe, affixed with a 27-gauge x ½-inch needle with a blue plunger rod.

2 Single Unit Syringes	NDC 55111-678-02
10 Single Unit Syringes	NDC 55111-678-10

5 mg fondaparinux sodium in 0.4 mL single dose prefilled syringe, affixed with a 27-gauge x ½-inch needle with an orange plunger rod.

2 Single Unit Syringes	NDC 55111-679-02
10 Single Unit Syringes	NDC 55111-679-10

7.5 mg fondaparinux sodium in 0.6 mL single dose prefilled syringe, affixed with a 27-gauge x ½-inch needle with a magenta plunger rod.

2 Single Unit Syringes	NDC 55111-680-02
10 Single Unit Syringes	NDC 55111-680-10

10 mg fondaparinux sodium in 0.8 mL single dose prefilled syringe, affixed with a 27-gauge x ½-inch needle with a violet plunger rod.

2 Single Unit Syringes	NDC 55111-681-02
10 Single Unit Syringes	NDC 55111-681-10

Store at 20°-25°C (68°-77°F); [see USP Controlled Room Temperature].

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 back pain, tingling, numbness (especially in the lower limbs), muscular weakness, and stool or urine incontinence. 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 fondaparinux sodium 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 fondaparinux sodium (e.g., if fondaparinux sodium is used at home), they should be advised of the following:

- Fondaparinux sodium 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 fondaparinux sodium 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 fondaparinux sodium.
- 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 fondaparinux sodium 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.

Rx Only

Manufactured by:
Gland Pharma Limited
D.P. Pally – 500 043 INDIA
Manufactured for:
Dr. Reddy's Laboratories Limited
Bachepalli – 502 325 INDIA

Revised: 0914



PATIENT INFORMATION

Fondaparinux Sodium Injection

Read the Patient Information that comes with fondaparinux sodium injection 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 fondaparinux sodium injection, ask your doctor or pharmacist.

What is the most important information I should know about fondaparinux sodium injection?

Spinal or epidural blood clots (hematoma). People who take a blood thinner medicine (anticoagulant) like fondaparinux sodium injection, and have medicine injected into their spinal and epidural area, or have a spinal puncture have a risk of forming a blood clot that can cause long-term or permanent loss of the ability to move (paralysis). Your risk of developing a spinal or epidural blood clot is higher if:

- a thin tube called an epidural catheter is placed in your back to give you certain medicine.
- you take NSAIDs or a medicine to prevent blood from clotting
- you have a history of difficult or repeated epidural or spinal punctures
- you have a history of problems with your spine or have had surgery on your spine.

If you take fondaparinux sodium injection and receive spinal anesthesia or have a spinal puncture, your doctor should watch you closely for symptoms of spinal or epidural blood clots. Tell your doctor right away if you have back pain, tingling, numbness, muscle weakness (especially in your legs and feet), loss of control of the bowels or bladder (incontinence).

Because the risk of bleeding may be higher, tell your doctor before taking fondaparinux sodium 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 fondaparinux sodium injection?

Fondaparinux sodium injection is a prescription medicine that “thins your blood” (also known as an anticoagulant). Fondaparinux sodium injection 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 fondaparinux sodium injection is safe and effective for use in children younger than 18 years of age.

Who should not take fondaparinux sodium injection?

Do not take fondaparinux sodium injection 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 fondaparinux sodium injection.

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

What should I tell my doctor before taking fondaparinux sodium injection?

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
- are pregnant. It is not known if fondaparinux sodium injection 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 fondaparinux sodium injection 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 fondaparinux sodium injection?”** 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 fondaparinux sodium injection, 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 fondaparinux sodium injection?

- Take fondaparinux sodium injection exactly as prescribed by your doctor.
- Fondaparinux sodium is given by injection under the skin (subcutaneous injection). See **“How should I give an injection of fondaparinux sodium?”**

- If your doctor tells you that you may give yourself injections of fondaparinux sodium 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 fondaparinux sodium injection.
- If you miss a dose of fondaparinux sodium injection, take your dose as soon as you remember. Do not take 2 doses at the same time.
- If you take too much fondaparinux sodium injection, call your doctor right away.
- Do not use fondaparinux sodium injection 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 fondaparinux sodium injection?

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

- **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 fondaparinux sodium injection.** Your doctor may check your kidney function while you are taking fondaparinux sodium injection.
- **People undergoing surgery who weigh less than 110 pounds.** See “Who should not take fondaparinux sodium injection?”
- **Low blood platelets.** Low blood platelets can happen when you take fondaparinux sodium injection. Platelets are blood cells that help your blood to clot normally. Your doctor may check your platelet counts while you take fondaparinux sodium injection. You may bruise or bleed more easily while taking fondaparinux sodium injection, 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 fondaparinux sodium injection.

- 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 fondaparinux sodium injection?” Serious allergic reactions can happen when you take fondaparinux sodium injection. If you experience swelling of the face or mouth or have difficulty in swallowing or breathing, contact your doctor right away. You should stop fondaparinux sodium injection if this happens.

Other side effects include:

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

These are not all the possible side effects of fondaparinux sodium injection. 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 fondaparinux sodium injection?

Store fondaparinux sodium injection at 20°-25°C (68°-77°F); [room temperature].

Safely, throw away fondaparinux sodium injection that is out of date or no longer needed.

Keep fondaparinux sodium injection and all medicines out of the reach of children.

General information about fondaparinux sodium injection

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

This leaflet summarizes the most important information about fondaparinux sodium injection. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about fondaparinux sodium injection that is written for healthcare professionals. For more information about fondaparinux sodium injection, call 1-888-375-3784.

What are the ingredients in fondaparinux sodium injection?

Active Ingredient: fondaparinux sodium

Inactive Ingredients: sodium chloride and water for injection. Also contain hydrochloric acid and sodium hydroxide as pH adjusters

How should I give an injection of fondaparinux sodium?

Fondaparinux sodium is injected into a skin fold of the lower stomach area (abdomen). Do not inject fondaparinux sodium 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. **The following instructions are specific to the Preventis™ injection system and may differ from the directions for other injection systems.** Be sure that you read, understand, and follow the step-by-step instructions in this leaflet, on how to give yourself an injection of fondaparinux sodium.

Instructions for self-administration

The different parts of fondaparinux sodium safety syringe are:

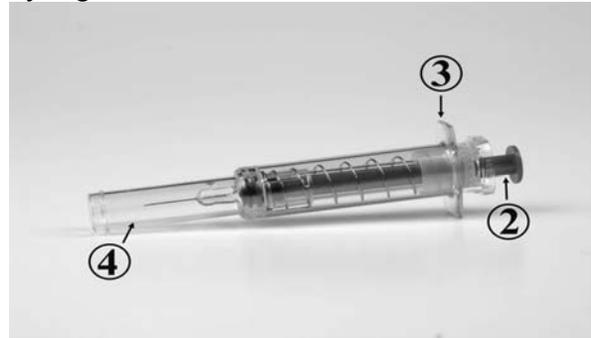
1. Rigid Needle Shield
2. Plunger
3. Finger-grip
4. Safety shield



Syringe BEFORE USE



Syringe AFTER USE



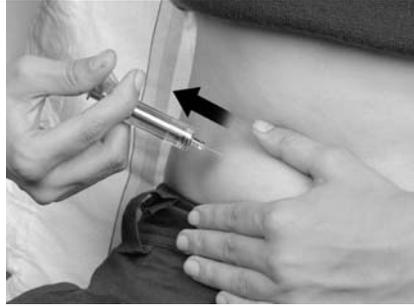
1. Wash your hands thoroughly with soap and water. Towel dry.
2. Sit or lie down in a comfortable position. Choose a spot on the lower stomach area (abdomen), at least 2 inches below your belly button (Figure A). Change (alternate) between using the left and right side of the lower abdomen for each injection. If you have any questions talk to your nurse or doctor.



Figure A.

3. Clean the injection area with an alcohol swab.

<p>4. Remove the needle shield by pulling it straight off the syringe (Figure B). Discard the needle shield.</p> <p>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.</p>	 <p style="text-align: right;">Figure B.</p>
<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 style="text-align: right;">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 style="text-align: right;">Figure D.</p>
<p>7. Inject all of the medicine in the syringe by pressing down on the plunger as far as it goes. (Figure E).</p>	 <p style="text-align: right;">Figure E.</p>

<p>8. Remove the syringe from the injection site keeping your finger on the plunger.</p>		<p>Figure F.</p>
<p>9. Orient the needle away from you and others, and activate the safety shield by firmly pushing the plunger. The protective sleeve will automatically cover the needle and an audible "click" will be heard to confirm shield activation.</p>		<p>Figure G.</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> <p>NOTE:</p> <ul style="list-style-type: none"> • The safety system can only be activated once the syringe has been emptied. • Activation of the safety system must be done only after removing the needle from the patient's skin. • Do not replace the needle shield after injection. • The safety system should not be sterilized. • Activation of the safety system may cause minimal splatter of fluid. For optimal safety activate the system while orienting it downwards away from yourself and others. 		

To reorder additional Patient Information Sheets contact Dr. Reddy's Customer Service at 1-866-733-3952 or visit www.reddyfondaparinux.com.

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Revised: 0914



HIGHLIGHTS OF PRESCRIBING INFORMATION

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

**SUMATRIPTAN Injection, USP
For Subcutaneous Use
Initial U.S. Approval: 1992**

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

Sumatriptan injection is a serotonin (5-HT_{1B/1D}) receptor agonist (triptan) indicated for:

- Acute treatment of migraine with or without aura in adults (1)
- Acute treatment of cluster headache in adults (1)

Limitations of Use:

- Use only if a clear diagnosis of migraine or cluster headache has been established. (1)
- Not indicated for the prevention of migraine attacks. (1)

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

- For subcutaneous use only. (2.1)
- Acute treatment of migraine: 1 to 6 mg single dose. (2.1)
- Acute treatment of cluster headache: 6 mg single dose. (2.1)
- Maximum dose in a 24-hour period: 12 mg, Separate doses by at least 1 hour. (2.1)
- Patients receiving doses other than 6 mg: Use the 6 mg single-dose vial. (2.3)

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

- Injection: 6 mg single-dose prefilled syringe assembled in an autoinjector (3)

-----CONTRAINDICATIONS-----

- Coronary artery disease or coronary vasospasm (4)
- Wolff-Parkinson-White syndrome or other cardiac accessory conduction pathway disorders (4)
- History of stroke, transient ischemic attack, or hemiplegic or basilar migraine (4)
- Peripheral vascular disease (4)
- Ischemic bowel disease (4)
- Uncontrolled hypertension (4)
- Recent (within 24 hours) use of another 5-HT₁ agonist (e.g., another triptan) or of an ergotamine-containing medication (4)

- Concurrent or recent (past 2 weeks) use of monoamine oxidase-A inhibitor (4)
- Known hypersensitivity to sumatriptan (4)
- Severe hepatic impairment (4)

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

- Myocardial ischemia/infarction and Prinzmetal’s angina: Perform cardiac evaluation in patients with multiple cardiovascular risk factors. (5.1)
- Arrhythmias: Discontinue sumatriptan injection if occurs. (5.2)
- Chest/throat/neck/jaw pain, tightness, pressure, or heaviness: Generally not associated with myocardial ischemia; evaluate for coronary artery disease in patients at high risk. (5.3)
- Cerebral hemorrhage, subarachnoid hemorrhage, and stroke: Discontinue sumatriptan injection if occurs. (5.4)
- Gastrointestinal ischemia and infarction events, peripheral vasospastic reactions: Discontinue sumatriptan injection if occurs. (5.5)
- Medication overuse headache: Detoxification may be necessary. (5.6)
- Serotonin syndrome: Discontinue sumatriptan injection if occurs. (5.7)
- Increase in blood pressure: Monitor blood pressure. (5.8)
- Anaphylactic/anaphylactoid reactions: Discontinue sumatriptan injection if occurs (5.9)
- Seizures: Use with caution in patients with epilepsy or a lowered seizure threshold. (5.10)

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

Most common adverse reactions (≥5% and > placebo) were injection site reactions, tingling, dizziness/vertigo, warm/hot sensation, burning sensation, feeling of heaviness, pressure sensation, flushing, feeling of tightness, and numbness (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Dr. Reddy’s Laboratories Inc. at 1-888-375-3784 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

- Pregnancy: Based on animal data, may cause fetal harm (8.1)
- Geriatric use: A cardiovascular evaluation is recommended in those who have other cardiovascular risk factors prior to receiving sumatriptan injection. (8.5)

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

Revised: 03/2015

**FULL PRESCRIBING INFORMATION:
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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Sumatriptan injection is indicated in adults for (1) the acute treatment of migraine, with or without aura, and (2) the acute treatment of cluster headache.

Limitations of Use:

- Use only if a clear diagnosis of migraine or cluster headache has been established.
- If a patient has no response to the first migraine attack treated with sumatriptan injection, reconsider the diagnosis of migraine before sumatriptan injection is administered to treat any subsequent attacks.
- Sumatriptan injection, is not indicated for the prevention of migraine attacks.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The maximum single recommended adult dose of sumatriptan injection for the acute treatment of migraine or cluster headache is 6 mg injected subcutaneously. For the treatment of migraine, if side effects are dose limiting, lower doses (1 to 5 mg) may be used [*see Clinical Studies (14.1)*]. For the treatment of cluster headache, the efficacy of lower doses has not been established.

The maximum cumulative dose that may be given in 24 hours is 12 mg, two 6 mg injections separated by at least 1 hour. A second 6 mg dose should only be considered if some response to a first injection was observed.

2.2 Administration Using the Autoinjector

An autoinjector device is available for use with a 6 mg prefilled syringe to facilitate self-administration in patients using the 6 mg dose. With this device, the needle penetrates approximately 1/4 inch (5 to 6 mm). The injection is intended to be given subcutaneously, and intramuscular or intravascular delivery should be avoided. Instruct patients on the proper use of the sumatriptan autoinjector and direct them to use injection sites with an adequate skin and subcutaneous thickness to accommodate the length of the needle.

2.3 Administration of Doses of Sumatriptan Injection Other Than 6 mg

In patients receiving doses other than 6 mg, use the 6 mg single-dose vial; do not use the Sumatriptan Autoinjector Pen. Visually inspect the vial for particulate matter and discoloration before administration. Do not use if particulates and discolorations are noted.

3 DOSAGE FORMS AND STRENGTHS

- Injection: 6 mg prefilled syringe assembled in an autoinjector

4 CONTRAINDICATIONS

Sumatriptan injection is contraindicated in patients with:

- Ischemic coronary artery disease (CAD) (angina pectoris, history of myocardial infarction, or documented silent ischemia) or coronary artery vasospasm, including Prinzmetal's angina [see *Warnings and Precautions* (5.1)].
- Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders [see *Warnings and Precautions* (5.2)].
- History of stroke or transient ischemic attack (TIA) because these patients are at a higher risk of stroke [see *Warnings and Precautions* (5.4)].
- History of hemiplegic or basilar migraine.
- Peripheral vascular disease [see *Warnings and Precautions* (5.5)].
- Ischemic bowel disease [see *Warnings and Precautions* (5.5)].
- Uncontrolled hypertension [see *Warnings and Precautions* (5.8)].
- Recent (i.e., within 24 hours) use of ergotamine-containing medication, ergot-type medication (such as dihydroergotamine or methysergide), or another 5-hydroxytryptamine₁ (5-HT₁) agonist [see *Drug Interactions* (7.1, 7.3)].
- Concurrent administration of an MAO-A inhibitor or recent (within 2 weeks) use of an MAO-A inhibitor [see *Drug Interactions* (7.2) and *Clinical Pharmacology* (12.3)].
- Known hypersensitivity to sumatriptan [see *Warnings and Precautions* (5.9) and *Adverse Reactions* (6.2)].
- Severe hepatic impairment [see *Clinical Pharmacology* (12.3)].

5 WARNINGS AND PRECAUTIONS

5.1 Myocardial Ischemia, Myocardial Infarction, and Prinzmetal's Angina

The use of sumatriptan injection is contraindicated in patients with ischemic or vasospastic CAD. There have been rare reports of serious cardiac adverse reactions, including acute myocardial infarction, occurring within a few hours following administration of sumatriptan injection. Some of these reactions occurred in patients without known CAD. 5-HT₁ agonists, including sumatriptan injection, may cause coronary artery vasospasm (Prinzmetal's angina), even in patients without a history of CAD.

Perform a cardiovascular evaluation in triptan-naive patients who have multiple cardiovascular risk factors (e.g., increased age, diabetes, hypertension, smoking, obesity, strong family history of CAD) prior to receiving sumatriptan injection. If there is evidence of CAD or coronary artery vasospasm, sumatriptan injection is contraindicated. For patients with multiple cardiovascular risk factors who have a negative cardiovascular evaluation, consider administering the first dose of sumatriptan injection in a medically supervised setting and performing an electrocardiogram (ECG) immediately following sumatriptan injection. For such patients, consider periodic cardiovascular evaluation in intermittent long-term users of sumatriptan injection.

Evaluate patients with signs or symptoms suggestive of angina following sumatriptan injection for the presence of CAD or Prinzmetal's angina before receiving additional doses of sumatriptan injection.

5.2 Arrhythmias

Life-threatening disturbances of cardiac rhythm, including ventricular tachycardia and ventricular fibrillation leading to death, have been reported within a few hours following the administration of 5-HT₁ agonists. Discontinue sumatriptan injection if these disturbances occur. Sumatriptan injection is contraindicated in patients with Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders.

5.3 Chest, Throat, Neck, and/or Jaw Pain/Tightness/Pressure

As with other 5-HT₁ agonists, sensations of tightness, pain, pressure, and heaviness in the precordium, throat, neck, and jaw commonly occur after treatment with sumatriptan injection and are usually non-cardiac in origin. However, perform a cardiac evaluation if these patients are at high cardiac risk. The use of sumatriptan injection is contraindicated in patients shown to have CAD and those with Prinzmetal's variant angina.

5.4 Cerebrovascular Events

Cerebral hemorrhage, subarachnoid hemorrhage, and stroke have occurred in patients treated with 5-HT₁ agonists, and some have resulted in fatalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the 5-HT₁ agonist having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine when they were not. Also, patients with migraine may be at increased risk of certain cerebrovascular events (e.g., stroke, hemorrhage, TIA). Discontinue sumatriptan injection if a cerebrovascular event occurs.

As with other acute migraine therapies, before treating headaches in patients not previously diagnosed as migraineurs, and in migraineurs who present with atypical symptoms, exclude other potentially serious neurological conditions. Sumatriptan injection is contraindicated in patients with a history of stroke or TIA.

5.5 Other Vasospasm Reactions

5-HT₁ agonists, including sumatriptan injection, may cause non-coronary vasospastic reactions, such as peripheral vascular ischemia, gastrointestinal vascular ischemia and infarction (presenting with abdominal pain and bloody diarrhea), splenic infarction, and Raynaud's syndrome. Until further evaluation, sumatriptan injection is contraindicated in patients who experience symptoms or signs suggestive of non-coronary vasospasm reaction following the use of any 5-HT₁ agonist.

Reports of transient and permanent blindness and significant partial vision loss have been reported with the use of 5-HT₁ agonists. Since visual disorders may be part of a migraine attack, a causal relationship between these events and the use of 5-HT₁ agonists have not been clearly established.

5.6 Medication Overuse Headache

Overuse of acute migraine drugs (e.g., ergotamine, triptans, opioids, combination of drugs for 10 or more days per month) may lead to exacerbation of headache (medication overuse headache). Medication overuse headache may present as migraine-like daily headaches or as a marked increase in frequency of migraine attacks. Detoxification of patients, including withdrawal of the

overused drugs, and treatment of withdrawal symptoms (which often includes a transient worsening of headache) may be necessary.

5.7 Serotonin Syndrome

Serotonin syndrome may occur with triptans, including sumatriptan injection, particularly during coadministration with selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and MAO inhibitors [see *Drug Interactions (7.4)*]. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g. hyperreflexia, incoordination), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). The onset of symptoms usually occurs within minutes to hours of receiving a new or a greater dose of a serotonergic medication. Discontinue sumatriptan injection if serotonin syndrome is suspected.

5.8 Increase in Blood Pressure

Significant elevation in blood pressure, including hypertensive crisis with acute impairment of organ systems, has been reported on rare occasions in patients treated with 5-HT₁ agonists, including patients without a history of hypertension. Monitor blood pressure in patients treated with sumatriptan. Sumatriptan injection is contraindicated in patients with uncontrolled hypertension.

5.9 Anaphylactic/Anaphylactoid Reactions

Anaphylactic/anaphylactoid reactions have occurred in patients receiving sumatriptan. Such reactions can be life threatening or fatal. In general, anaphylactic reactions to drugs are more likely to occur in individuals with a history of sensitivity to multiple allergens. Sumatriptan injection is contraindicated in patients with prior serious anaphylactic reaction.

5.10 Seizures

Seizures have been reported following administration of sumatriptan. Some have occurred in patients with either a history of seizures or concurrent conditions predisposing to seizures. There are also reports in patients where no such predisposing factors are apparent. Sumatriptan injection should be used with caution in patients with a history of epilepsy or conditions associated with a lowered seizure threshold.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Myocardial ischemia, myocardial infarction, and Prinzmetal's angina [see *Warnings and Precautions (5.1)*]
- Arrhythmias [see *Warnings and Precautions (5.2)*]
- Chest, throat, neck, and/or jaw pain/tightness/pressure [see *Warnings and Precautions (5.3)*]
- Cerebrovascular events [see *Warnings and Precautions (5.4)*]
- Other vasospasm reactions [see *Warnings and Precautions (5.5)*]
- Medication overuse headache [see *Warnings and Precautions (5.6)*]
- Serotonin syndrome [see *Warnings and Precautions (5.7)*]

- Increase in blood pressure [see Warnings and Precautions (5.8)]
- Anaphylactic/anaphylactoid reactions [see Warnings and Precautions (5.9)]
- Seizures [see Warnings and Precautions (5.10)]

6.1 Clinical Trials Experience

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

Migraine Headache: Table 1 lists adverse reactions that occurred in 2 U.S. placebo-controlled clinical trials in migraine subjects [Studies 2 and 3, see Clinical Studies (14.1)] following either a single 6 mg dose of sumatriptan injection or placebo. Only reactions that occurred at a frequency of 2% or more in groups treated with sumatriptan injection 6 mg and that occurred at a frequency greater than the placebo group are included in Table 1.

Table 1. Adverse Reactions Reported by at Least 2% of Subjects and at a Greater Frequency than Placebo in 2 Placebo-Controlled Migraine Clinical Trials (Studies 2 and 3)^a

Adverse Reaction	Percent of Subjects Reporting	
	Sumatriptan Injection 6 mg Subcutaneous (n = 547)	Placebo (n = 370)
Atypical sensations	42	9
Tingling	14	3
Warm/hot sensation	11	4
Burning sensation	7	<1
Feeling of heaviness	7	1
Pressure sensation	7	2
Feeling of tightness	5	<1
Numbness	5	2
Feeling stran	2	<1
Tight feeling in head	2	<1
Cardiovascular		
Flushing	7	2
Chest discomfort	5	1
Tightness in chest	3	<1
Pressure in chest	2	<1
Ear, nose, and throat		
Throat discomfort	3	<1
Discomfort: nasal cavity/sinuses	2	<1
Injection site reaction ^b	59	24

Miscellaneous Jaw discomfort	2	0
Musculoskeletal Weakness	5	<1
Neck pain/stiffness	5	<1
Myalgia	2	<1
Neurological Dizziness/vertigo	12	4
Drowsiness/sedation	3	2
Headache	2	<1
Skin Sweating	2	1

^a The sum of the percentages cited is greater than 100% because subjects may have experienced more than 1 type of adverse reaction. Only reactions that occurred at a frequency of 2% or more in groups treated with sumatriptan injection and occurred at a frequency greater than the placebo groups are included.

^b Includes injection site pain, stinging/burning, swelling, erythema, bruising, bleeding.

The incidence of adverse reactions in controlled clinical trials was not affected by gender or age of the subjects. There were insufficient data to assess the impact of race on the incidence of adverse reactions.

Cluster Headache: In the controlled clinical trials assessing the efficacy of sumatriptan injection as a treatment for cluster headache [Studies 4 and 5, *see Clinical Studies (14.2)*], no new significant adverse reactions were detected that had not already been identified in trials of sumatriptan injection in subjects with migraine.

Overall, the frequency of adverse reactions reported in the trials of cluster headache was generally lower than in the migraine trials. Exceptions include reports of paresthesia (5% sumatriptan injection, 0% placebo), nausea and vomiting (4% sumatriptan injection, 0% placebo), and bronchospasm (1% sumatriptan injection, 0% placebo).

Other Adverse Reactions: In the paragraphs that follow, the frequencies of less commonly reported adverse reactions are presented. Reaction frequencies were calculated as the number of subjects reporting a reaction divided by the total number of subjects (N = 6,218) exposed to subcutaneous sumatriptan injection. All reported reactions are included except those already listed in the previous table. Reactions are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent are defined as those occurring in at least 1/100 subjects, infrequent are those occurring in 1/100 to 1/1,000 subjects, and rare are those occurring in fewer than 1/1,000 subjects.

Cardiovascular: Infrequent were hypertension, hypotension, bradycardia, tachycardia, palpitations, and syncope. Rare was arrhythmia.

Gastrointestinal: Frequent was abdominal discomfort.

Musculoskeletal: Frequent were muscle cramps.

Neurological: Frequent was anxiety. Infrequent were mental confusion, euphoria, agitation, tremor. Rare were myoclonia, sleep disturbance, and dystonia.

Respiratory: Infrequent was dyspnea.

Skin: Infrequent were erythema, pruritus, and skin rashes.

Miscellaneous: Infrequent was “serotonin agonist effect”.

Adverse Events Observed With Other Formulations of Sumatriptan: The following adverse events occurred in clinical trials with sumatriptan tablets and sumatriptan nasal spray.

Because the reports include events observed in open and uncontrolled trials, the role of sumatriptan injection in their causation cannot be reliably determined. All reported events are included except those already listed, those too general to be informative, and those not reasonably associated with the use of the drug.

Cardiovascular: Angina, cerebrovascular lesion, heart block, peripheral cyanosis, phlebitis, thrombosis.

Gastrointestinal: Abdominal distention and colitis.

Neurological: Convulsions, hallucinations, syncope, suicide, and twitching.

Miscellaneous: Edema, hypersensitivity, swelling of extremities, and swelling of face.

6.2 Post marketing Experience

The following adverse reactions have been identified during postapproval use of sumatriptan tablets, sumatriptan nasal spray, and sumatriptan injection. 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. These reactions have been chosen for inclusion due to either their seriousness, frequency of reporting, or causal connection to sumatriptan or a combination of these factors.

Blood: Hemolytic anemia, pancytopenia, thrombocytopenia.

Ear, Nose, and Throat: Deafness.

Eye: Ischemic optic neuropathy, retinal artery occlusion, retinal vein thrombosis.

Neurological: Central nervous system vasculitis, cerebrovascular accident, serotonin syndrome, subarachnoid hemorrhage.

Non-Site Specific: Angioedema, cyanosis, temporal arteritis.

Skin: Exacerbation of sunburn, hypersensitivity reactions (allergic vasculitis, erythema, pruritus, rash, shortness of breath, urticaria), photosensitivity. Following subcutaneous administration of sumatriptan injection, pain, redness, stinging, induration, swelling, contusion, subcutaneous bleeding, and, on rare occasions, lipoatrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue) have been reported.

Urogenital: Acute renal failure.

7 DRUG INTERACTIONS

7.1 Ergot-Containing Drugs

Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because these effects may be additive, use of ergotamine-containing or ergot-type medications (like dihydroergotamine or methysergide) and sumatriptan injection within 24 hours of each other is contraindicated.

7.2 Monoamine Oxidase-A Inhibitors

MAO-A inhibitors increase systemic exposure by 2-fold. Therefore, the use of sumatriptan injection in patients receiving MAO-A inhibitors is contraindicated [*see Clinical Pharmacology (12.3)*].

7.3 Other 5-HT₁ Agonists

Because their vasospastic effects may be additive, coadministration of sumatriptan injection and other 5-HT₁ agonists (e.g., triptans) within 24 hours of each other is contraindicated.

7.4 Selective Serotonin Reuptake Inhibitors/Serotonin Norepinephrine Reuptake Inhibitors and Serotonin Syndrome

Cases of serotonin syndrome have been reported during coadministration of triptans and SSRIs, or SNRIs, TCAs, and MAO inhibitors [*see Warnings and Precautions (5.7)*].

8 USES IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: There are no adequate and well-controlled trials of sumatriptan injection in pregnant women. Sumatriptan injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

When sumatriptan was administered intravenously to pregnant rabbits daily throughout the period of organogenesis, embryoletality was observed at doses at or close to those producing maternal toxicity. These doses were less than the maximum recommended human dose (MRHD) of 12 mg/day on a mg/m² basis. Oral administration of sumatriptan to rabbits during organogenesis was associated with increased incidences of fetal vascular and skeletal abnormalities. The highest no-effect dose for these effects was 15 mg/kg/day. The intravenous

administration of sumatriptan to pregnant rats throughout organogenesis at doses that are approximately 10 times the MRHD on a mg/m² basis, did not produce evidence of embryoletality. The subcutaneous administration of sumatriptan to pregnant rats prior to and throughout pregnancy did not produce evidence of embryoletality or teratogenicity.

8.3 Nursing Mothers

It is not known whether sumatriptan is excreted in human breast milk following subcutaneous administration. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from sumatriptan injection, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

Safety and effectiveness of sumatriptan injection in pediatric patients under 18 years of age have not been established; therefore, sumatriptan injection is not recommended for use in patients under 18 years of age.

Two controlled clinical trials evaluated sumatriptan nasal spray (5 to 20 mg) in 1,248 adolescent migraineurs aged 12 to 17 years who treated a single attack. The trials did not establish the efficacy of sumatriptan nasal spray compared with placebo in the treatment of migraine in adolescents. Adverse reactions observed in these clinical trials were similar in nature to those reported in clinical trials in adults.

Five controlled clinical trials (2 single-attack trials, 3 multiple-attack trials) evaluating oral sumatriptan (25 to 100 mg) in pediatric subjects aged 12 to 17 years enrolled a total of 701 adolescent migraineurs. These trials did not establish the efficacy of oral sumatriptan compared with placebo in the treatment of migraine in adolescents. Adverse reactions observed in these clinical trials were similar in nature to those reported in clinical trials in adults. The frequency of all adverse reactions in these subjects appeared to be both dose- and age-dependent, with younger subjects reporting reactions more commonly than older adolescents.

Postmarketing experience documents that serious adverse reactions have occurred in the pediatric population after use of subcutaneous, oral, and/or intranasal sumatriptan. These reports include reactions similar in nature to those reported rarely in adults, including stroke, visual loss, and death. A myocardial infarction has been reported in a 14-year-old male following the use of oral sumatriptan; clinical signs occurred within 1 day of drug administration. Since clinical data to determine the frequency of serious adverse reactions in pediatric patients who might receive subcutaneous, oral, or intranasal sumatriptan are not presently available, the use of sumatriptan in patients under 18 years of age is not recommended.

8.5 Geriatric Use

Clinical trials of sumatriptan injection did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger subjects. In general, dose selection for an elderly patient should be cautious, usually starting at

the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

A cardiovascular evaluation is recommended for geriatric patients who have other cardiovascular risk factors (e.g., diabetes, hypertension, smoking, obesity, strong family history of CAD) prior to receiving sumatriptan injection [see *Warnings and Precautions (5.1)*].

10 OVERDOSAGE

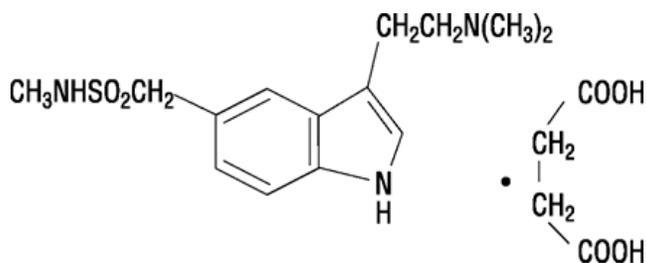
No gross overdoses in clinical practice have been reported. Coronary vasospasm was observed after intravenous administration of sumatriptan injection [see *Contraindications (4)*]. Overdoses would be expected from animal data (dogs at 0.1 g/kg, rats at 2 g/kg) to possibly cause convulsions, tremor, inactivity, erythema of the extremities, reduced respiratory rate, cyanosis, ataxia, mydriasis, injection site reactions (desquamation, hair loss, and scab formation), and paralysis.

The elimination half-life of sumatriptan is about 2 hours [see *Clinical Pharmacology (12.3)*], and therefore monitoring of patients after overdose with sumatriptan injection should continue for at least 10 hours or while symptoms or signs persist.

It is unknown what effect hemodialysis or peritoneal dialysis has on the serum concentrations of sumatriptan.

11 DESCRIPTION

Sumatriptan injection USP contains sumatriptan succinate, a selective 5-HT_{1B/1D} receptor agonist. Sumatriptan succinate is chemically designated as 3-[2-(dimethylamino)ethyl]-N-methyl-indole-5-methanesulfonamide succinate (1:1), and it has the following structure:



The molecular formula is C₁₄H₂₁N₃O₂S · C₄H₆O₄, representing a molecular weight of 413.5. Sumatriptan succinate USP is a white to off-white powder that is readily soluble in water and in saline.

Sumatriptan injection USP, is a clear, colorless to pale yellow, sterile, nonpyrogenic solution for subcutaneous injection. Each 0.5 mL of sumatriptan injection solution contains 6 mg of sumatriptan (base) as the succinate salt and 3.5 mg of sodium chloride, USP in Water for Injection, USP. The pH range of the solutions is approximately 4.2 to 5.3. The osmolality of the injection is between 275 and 315 mOsm/kg.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Sumatriptan binds with high affinity to human cloned 5-HT_{1B/1D} receptors. Sumatriptan presumably exerts its therapeutic effects in the treatment of migraine headache by binding to 5-HT_{1B/1D} receptors located on intracranial blood vessels and sensory nerves of the trigeminal system.

Current theories proposed to explain the etiology of migraine headache suggest that symptoms are due to local cranial vasodilatation and/or to the release of sensory neuropeptides (including substance P and calcitonin gene-related peptide) through nerve endings in the trigeminal system. The therapeutic activity of sumatriptan for the treatment of migraine and cluster headaches is thought to be due to the agonist effects at the 5-HT_{1B/1D} receptors on intracranial blood vessels (including the arterio-venous anastomoses) and sensory nerves of the trigeminal system, which result in cranial vessel constriction and inhibition of pro-inflammatory neuropeptide release.

12.2 Pharmacodynamics

Blood Pressure: Significant elevation in blood pressure, including hypertensive crisis, has been reported in patients with and without a history of hypertension [*see Warnings and Precautions (5.8)*].

Peripheral (Small) Arteries: In healthy volunteers (N = 18), a trial evaluating the effects of sumatriptan on peripheral (small vessel) arterial reactivity failed to detect a clinically significant increase in peripheral resistance.

Heart Rate: Transient increases in blood pressure observed in some subjects in clinical trials carried out during sumatriptan's development as a treatment for migraine were not accompanied by any clinically significant changes in heart rate.

12.3 Pharmacokinetics

Absorption and Bioavailability: The bioavailability of sumatriptan via subcutaneous site injection to 18 healthy male subjects was 97% ± 16% of that obtained following intravenous injection.

After a single 6 mg subcutaneous manual injection into the deltoid area of the arm in 18 healthy males (age: 24 ± 6 years, weight: 70 kg), the maximum serum concentration (C_{max}) of sumatriptan was (mean ± standard deviation) 74 ± 15 ng/mL and the time to peak concentration (T_{max}) was 12 minutes after injection (range: 5 to 20 minutes). In this trial, the same dose injected subcutaneously in the thigh gave a C_{max} of 61 ± 15 ng/mL by manual injection versus 52 ± 15 ng/mL by autoinjector techniques. The T_{max} or amount absorbed was not significantly altered by either the site or technique of injection.

Distribution: Protein binding, determined by equilibrium dialysis over the concentration range of 10 to 1,000 ng/mL, is low, approximately 14% to 21%. The effect of sumatriptan on the protein binding of other drugs has not been evaluated.

Following a 6 mg subcutaneous injection into the deltoid area of the arm in 9 males (mean age: 33 years, mean weight: 77 kg) the volume of distribution central compartment of sumatriptan was 50 ± 8 liters and the distribution half-life was 15 ± 2 minutes.

Metabolism: *In vitro* studies with human microsomes suggest that sumatriptan is metabolized by MAO, predominantly the A isoenzyme. Most of a radiolabeled dose of sumatriptan excreted in the urine is the major metabolite indole acetic acid (IAA) or the IAA glucuronide, both of which are inactive.

Elimination: After a single 6 mg subcutaneous dose, $22\% \pm 4\%$ was excreted in the urine as unchanged sumatriptan and $38\% \pm 7\%$ as the IAA metabolite.

Following a 6 mg subcutaneous injection into the deltoid area of the arm, the systemic clearance of sumatriptan was $1,194 \pm 149$ mL/min and the terminal half-life was 115 ± 19 minutes.

Special Populations: *Age:* The pharmacokinetics of sumatriptan in the elderly (mean age: 72 years, 2 males and 4 females) and in subjects with migraine (mean age: 38 years, 25 males and 155 females) were similar to that in healthy male subjects (mean age: 30 years).

Renal Impairment: The effect of renal impairment on the pharmacokinetics of sumatriptan has not been examined.

Hepatic Impairment: The effect of mild to moderate hepatic disease on the pharmacokinetics of subcutaneously administered sumatriptan has been evaluated. There were no significant differences in the pharmacokinetics of subcutaneously administered sumatriptan in moderately hepatically impaired subjects compared with healthy controls. The pharmacokinetics of subcutaneously administered sumatriptan in patients with severe hepatic impairment has not been studied. The use of sumatriptan injection in this population is contraindicated [*see Contraindications (4)*].

Race: The systemic clearance and C_{max} of sumatriptan were similar in black (n = 34) and Caucasian (n = 38) healthy male subjects.

Drug Interaction Studies: Monoamine Oxidase-A Inhibitors: In a trial of 14 healthy females, pretreatment with an MAO-A inhibitor decreased the clearance of sumatriptan, resulting in a 2-fold increase in the area under the sumatriptan plasma concentration-time curve (AUC), corresponding to a 40% increase in elimination half-life.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: In carcinogenicity studies, rats and mice were given sumatriptan by oral gavage. Mice were dosed for 78 weeks and rats were dosed for 104 weeks. Average exposures achieved in mice receiving the highest dose were approximately 110 times the exposure attained in humans after the maximum recommended single dose of 6 mg. The highest dose to rats was

approximately 260 times the maximum single dose of 6 mg on a mg/m² basis. There was no evidence of an increase in tumors in either species related to sumatriptan administration.

Mutagenesis: Sumatriptan was not mutagenic in the presence or absence of metabolic activation when tested in 2 gene mutation assays (the Ames test and the *in vitro* mammalian Chinese hamster V79/HGPRT assay). It was not clastogenic in 2 cytogenetics assays (the *in vitro* human lymphocyte assay and the *in vivo* rat micronucleus assay).

Impairment of Fertility: A fertility study (Segment I) by the subcutaneous route, during which male and female rats were dosed daily with sumatriptan prior to and throughout the mating period, has shown no evidence of impaired fertility at doses equivalent to approximately 100 times the maximum recommended single human dose of 6 mg on a mg/m² basis. However, following oral administration, a treatment-related decrease in fertility, secondary to a decrease in mating, was seen for rats treated with 50 and 500 mg/kg/day. The no-effect dose for this finding was approximately 8 times the maximum recommended single human dose of 6 mg on a mg/m² basis. It is not clear whether the problem is associated with the treatment of males or females or both.

13.2 Animal Toxicology and/or Pharmacology

Corneal Opacities: Dogs receiving oral sumatriptan developed corneal opacities and defects in the corneal epithelium. Corneal opacities were seen at the lowest dosage tested, 2 mg/kg/day, and were present after 1 month of treatment. Defects in the corneal epithelium were noted in a 60 week study. Earlier examinations for these toxicities were not conducted and no-effect doses were not established; however, the relative exposure at the lowest dose tested was approximately 5 times the human exposure after a 100 mg oral dose or 3 times the human exposure after a 6 mg subcutaneous dose.

Melanin Binding: In rats with a single subcutaneous dose (0.5 mg/kg) of radiolabeled sumatriptan, the elimination half-life of radioactivity from the eye was 15 days, suggesting that sumatriptan and its metabolites bind to the melanin of the eye. The clinical significance of this binding is unknown.

14 CLINICAL STUDIES

14.1 Migraine

In controlled clinical trials enrolling more than 1,000 subjects during migraine attacks who were experiencing moderate or severe pain and 1 or more of the symptoms enumerated in Table 3, onset of relief began as early as 10 minutes following a 6 mg sumatriptan injection. Lower doses of sumatriptan injection may also prove effective, although the proportion of subjects obtaining adequate relief was decreased and the latency to that relief is greater with lower doses.

In Study 1, 6 different doses of sumatriptan injection (n = 30 each group) were compared with placebo (n = 62), in a single-attack, parallel-group design, the dose response relationship was found to be as shown in Table 2.

Table 2. Proportion of Subjects With Migraine Relief and Incidence of Adverse Events by Time and by Sumatriptan Dose in Study 1

Dose of Sumatriptan Injection	Percent Subjects With Relief ^a				Adverse Events Incidence (%)
	at 10 Minutes	at 30 Minutes	at 1 Hour	at 2 Hours	
Placebo	5	15	24	21	55
1 mg	10	40	43	40	63
2 mg	7	23	57	43	63
3 mg	17	47	57	60	77
4 mg	13	37	50	57	80
6 mg	10	63	73	70	83
8 mg	23	57	80	83	93

^a Relief is defined as the reduction of moderate or severe pain to no or mild pain after dosing without use of rescue medication.

In 2 randomized, placebo-controlled clinical trials of sumatriptan injection 6 mg in 1,104 subjects with moderate or severe migraine pain (Studies 2 and 3), the onset of relief was less than 10 minutes. Headache relief, as defined by a reduction in pain from severe or moderately severe to mild or no headache, was achieved in 70% of the subjects within 1 hour of a single 6 mg subcutaneous dose of sumatriptan injection. Approximately 82% and 65% of subjects treated with sumatriptan injection 6 mg had headache relief and were pain free within 2 hours, respectively.

Table 3 shows the 1- and 2-hour efficacy results for sumatriptan injection 6 mg in Studies 2 and 3.

Table 3. Proportion of Subjects with Pain Relief and Relief of Migraine Symptoms After 1 and 2 Hours of Treatment in Studies 2 and 3

1-Hour Data	Study 2		Study 3	
	Placebo (n = 190)	Sumatriptan Injection 6 mg (n = 384)	Placebo (n = 180)	Sumatriptan Injection 6 mg (n = 350)
Subjects with pain relief (grade 0/1)	18%	70% ^a	26%	70% ^a
Subjects with no pain	5%	48% ^a	13%	49% ^a
Subjects without nausea	48%	73% ^a	50%	73% ^a
Subjects without photophobia	23%	56% ^a	25%	58% ^a
Subjects with little or no clinical disability ^b	34%	76% ^a	34%	76% ^a

2-Hour Data	Study 2		Study 3	
	Placebo ^c	Sumatriptan Injection 6 mg ^d	Placebo ^c	Sumatriptan Injection 6 mg ^d
Subjects with pain relief (grade 0/1)	31%	81% ^a	39%	82% ^a
Subjects with no pain	11%	63% ^a	19%	65% ^a
Subjects without nausea	56%	82% ^a	63%	81% ^a
Subjects without photophobia	31%	72% ^a	35%	71% ^a
Subjects with little or no clinical disability ^b	42%	85% ^a	49%	84% ^a

^a $P < 0.05$ versus placebo.

^b A successful outcome in terms of clinical disability was defined prospectively as ability to work mildly impaired or ability to work and function normally.

^c Includes subjects that may have received an additional placebo injection 1 hour after the initial injection.

^d Includes subjects that may have received an additional 6 mg of sumatriptan injection 1 hour after the initial injection.

Sumatriptan injection also relieved photophobia, phonophobia (sound sensitivity), nausea, and vomiting associated with migraine attacks. Similar efficacy was seen when subjects self-administered sumatriptan injection using an autoinjector.

The efficacy of sumatriptan injection was unaffected by whether or not the migraine was associated with aura, duration of attack, gender or age of the subject, or concomitant use of common migraine prophylactic drugs (e.g., beta-blockers).

14.2 Cluster Headache

The efficacy of sumatriptan injection in the acute treatment of cluster headache was demonstrated in 2 randomized, double-blind, placebo-controlled, 2-period crossover trials (Studies 4 and 5). Subjects aged 21 to 65 years were enrolled and were instructed to treat a moderate to very severe headache within 10 minutes of onset. Headache relief was defined as a reduction in headache severity to mild or no pain. In both trials, the proportion of individuals gaining relief at 10 or 15 minutes was significantly greater among subjects receiving 6 mg of sumatriptan injection compared with those who received placebo (see Table 4).

Table 4. Proportion of Subjects With Cluster Headache Relief by Time in Studies 4 and 5

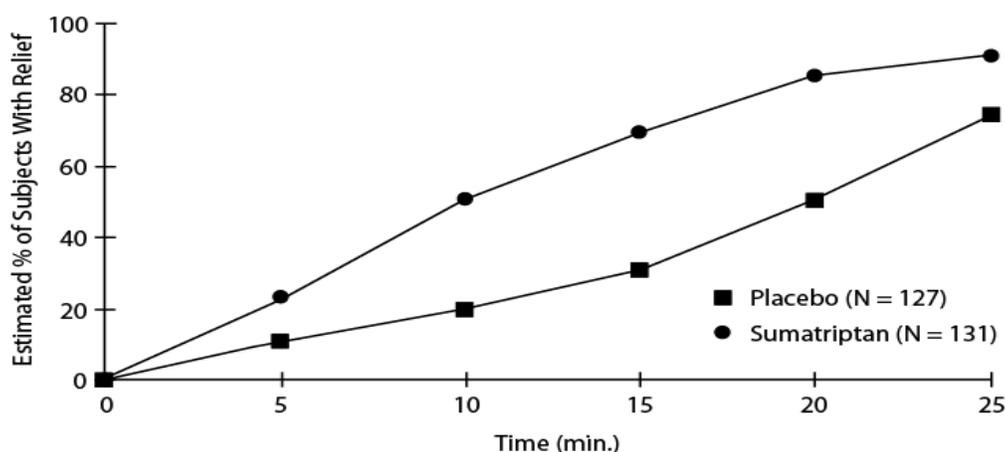
	Study 4		Study 5	
	Placebo (n = 39)	Sumatriptan Injection 6 mg (n = 39)	Placebo (n = 88)	Sumatriptan Injection 6 mg (n = 92)
Subjects with pain relief (no/mild)				
5 Minutes post-injection	8%	21%	7%	23% ^a
10 Minutes post-injection	10%	49% ^a	25%	49% ^a
15 Minutes post-injection	26%	74% ^a	35%	75% ^a

^a $P < 0.05$.

(n = Number of headaches treated.)

An estimate of the cumulative probability of a subject with a cluster headache obtaining relief after being treated with either sumatriptan injection or placebo is presented in Figure 1.

Figure 1. Time to Relief of Cluster Headache from Time of Injection^a



^a

The figure uses Kaplan-Meier (product limit) Survivorship Plot. Subjects taking rescue medication were censored at 15 minutes.

The plot was constructed with data from subjects who either experienced relief or did not require (request) rescue medication within a period of 2 hours following treatment. As a consequence, the data in the plot are derived from only a subset of the 258 headaches treated (rescue medication was required in 52 of the 127 placebo-treated headaches and 18 of the 131 headaches treated with sumatriptan injection).

Other data suggest that treatment with sumatriptan injection is not associated with an increase in early recurrence of headache and has little effect on the incidence of later-occurring headaches (i.e., those occurring after 2, but before 18 or 24 hours).

16 HOW SUPPLIED/STORAGE AND HANDLING

Sumatriptan injection USP contains sumatriptan (base) as the succinate salt and is supplied as a clear, colorless to pale yellow, sterile, nonpyrogenic solution as follows:

NDC 55111-693-12 Sumatriptan Injection USP Autoinjector System includes 2 Autoinjectors, each with an associated single-dose prefilled syringe which contains 6 mg of sumatriptan (as the succinate salt) and 3.5 mg of sodium chloride in 0.5 mL of solution.

Store at 25°C (77°F); excursions permitted 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from light.

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information and Instructions for Use).

17.1 Risk of Myocardial Ischemia and/or Infarction, Prinzmetal's Angina, Other Vasospasm-Related Events, Arrhythmias, and Cerebrovascular Events

Inform patients that sumatriptan injection may cause serious cardiovascular side effects such as myocardial infarction or stroke. Although serious cardiovascular events can occur without warning symptoms, patients should be alert for the signs and symptoms of chest pain, shortness of breath, irregular heartbeat, significant rise in blood pressure, weakness, and slurring of speech and should ask for medical advice when observing any indicative sign or symptoms. Patients should be apprised of the importance of this follow-up [see *Warnings and Precautions (5.1, 5.2, 5.4, 5.5, and 5.8)*].

17.2 Anaphylactic/Anaphylactoid Reactions

Inform patients that anaphylactic/anaphylactoid reactions have occurred in patients receiving sumatriptan injection. Such reactions can be life threatening or fatal. In general, anaphylactic reactions to drugs are more likely to occur in individuals with a history of sensitivity to multiple allergens [see *Warnings and Precautions (5.9)*].

17.3 Medication Overuse Headache

Inform patients that use of acute migraine drugs for 10 or more days per month may lead to an exacerbation of headache and encourage patients to record headache frequency and drug use (e.g., by keeping a headache diary) [see *Warnings and Precautions (5.6)*].

17.4 Pregnancy

Inform patients that sumatriptan injection should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus [see *Use in Specific Populations (8.1)*].

17.5 Nursing Mothers

Advise patients to notify their healthcare provider if they are breastfeeding or plan to breastfeed [see *Use in Specific Populations (8.3)*].

17.6 Ability To Perform Complex Tasks

Since migraines or treatment with sumatriptan injection may cause somnolence and dizziness, instruct patients to evaluate their ability to perform complex tasks during migraine attacks and after administration of sumatriptan injection.

17.7 Serotonin Syndrome

Patients should be cautioned about the risk of serotonin syndrome with the use of sumatriptan injection or other triptans, particularly during combined use with SSRIs, SNRIs, TCAs, and MAO inhibitors [see *Warnings and Precautions (5.7) and Drug Interactions (7.4)*].

17.8 How to Use Sumatriptan Injection

Provide patients instruction on the proper use of sumatriptan injection if they are able to self-administer sumatriptan injection in medically unsupervised situation.

Inform patient that the needle in the autoinjector penetrates approximately 1/4 of an inch (5 to 6 mm). Inform patients that the injection is intended to be given subcutaneously and intramuscular or intravascular delivery should be avoided. Instruct patients to use injection sites with an adequate skin and subcutaneous thickness to accommodate the length of the needle.

Rx Only

Manufactured by:
Gland Pharma Limited
D.P. Pally – 500 043 INDIA

Manufactured for:
Dr. Reddy's Laboratories Limited
Bachupally – 500 090 INDIA

Revised: 0315



PATIENT INFORMATION

Sumatriptan Injection USP

Read this Patient Information before you start taking sumatriptan and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or treatment.

What is the most important information I should know about sumatriptan injection?

Sumatriptan can cause serious side effects, including:

Heart attack and other heart problems. Heart problems may lead to death.

Stop taking sumatriptan and get emergency medical help right away if you have any of the following symptoms of a heart attack:

- discomfort in the center of your chest that lasts for more than a few minutes, or that goes away and comes back
- severe tightness, pain, pressure, or heaviness in your chest, throat, neck, or jaw
- pain or discomfort in your arms, back, neck, jaw, or stomach
- shortness of breath with or without chest discomfort
- breaking out in a cold sweat
- nausea or vomiting
- feeling lightheaded

Sumatriptan is not for people with risk factors for heart disease unless a heart exam is done and shows no problem. You have a higher risk for heart disease if you:

- have high blood pressure
- have high cholesterol levels
- smoke
- are overweight
- have diabetes
- have a family history of heart disease

What is sumatriptan?

Sumatriptan is a prescription medicine used to treat acute migraine headaches with or without aura and acute cluster headaches in adults who have been diagnosed with migraine or cluster headaches.

Sumatriptan is not used to treat other types of headaches such as hemiplegic (that make you unable to move on one side of your body) or basilar (rare form of migraine with aura) migraines.

Sumatriptan is not used to prevent or decrease the number of migraine or cluster headaches you have.

It is not known if sumatriptan is safe and effective in children under 18 years of age.

Who should not take sumatriptan injection?

Do not take sumatriptan injection if you have:

- heart problems or a history of heart problems
- narrowing of blood vessels to your legs, arms, stomach, or kidney (peripheral vascular disease)
- uncontrolled high blood pressure
- hemiplegic migraines or basilar migraines. If you are not sure if you have these types of migraines, ask your healthcare provider.
- had a stroke, transient ischemic attacks (TIAs), or problems with your blood circulation
- taken any of the following medicines in the last 24 hours:
 - almotriptan (AXERT[®])
 - eletriptan (RELPAX[®])
 - frovatriptan (FROVA[®])
 - naratriptan (AMERGE[®])
 - rizatriptan (MAXALT[®], MAXALT-MLT[®])
 - sumatriptan and naproxen (TREXIMET[®])
 - ergotamines (CAFERGOT[®], ERGOMAR[®], MIGERGOT[®])
 - dihydroergotamine (D.H.E. 45[®], MIGRANAL[®])

Ask your healthcare provider if you are not sure if your medicine is listed above.

- an allergy to sumatriptan or any of the ingredients in sumatriptan injection. See the end of this leaflet for a complete list of ingredients in sumatriptan injection.

What should I tell my healthcare provider before taking sumatriptan injection?

Before you take sumatriptan, tell your healthcare provider about all of your medical conditions, including if you:

- have high blood pressure
- have high cholesterol
- have diabetes
- smoke
- are overweight
- have heart problems or family history of heart problems or stroke
- have liver problems
- have had epilepsy or seizures
- are not using effective birth control
- become pregnant while taking sumatriptan
- are breastfeeding or plan to breastfeed. Sumatriptan passes into your breast milk and may harm your baby. Talk with your healthcare provider about the best way to feed your baby if you take sumatriptan.

Tell your healthcare provider about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements.

Using sumatriptan with certain other medicines can affect each other, causing serious side effects.

Especially tell your healthcare provider if you take antidepressant medicines called:

- selective serotonin reuptake inhibitors (SSRIs)
- serotonin norepinephrine reuptake inhibitors (SNRIs)
- tricyclic antidepressants (TCAs)
- monoamine oxidase inhibitors (MAOIs)

Ask your healthcare provider or pharmacist for a list of these medicines if you are not sure.

Know the medicines you take. Keep a list of them to show your healthcare provider or pharmacist when you get a new medicine.

How should I take sumatriptan injection?

- Certain people should take their first dose of sumatriptan injection in their healthcare provider's office or in another medical setting. Ask your healthcare provider if you should take your first dose in a medical setting.
- Use sumatriptan injection exactly as your healthcare provider tells you to use it.
- Your healthcare provider may change your dose. Do not change your dose without first talking with your healthcare provider.
- For adults, the usual dose is a single injection given just below the skin.
- You should give an injection as soon as the symptoms of your headache start, but it may be given at any time during a migraine attack.
- If you did not get any relief after the first injection, do not give a second injection without first talking with your healthcare provider.
- You can take a second injection 1 hour after the first injection, but not sooner, if your headache came back after your first injection.
- Do not take more than 12 mg in a 24 hour period.
- If you use too much sumatriptan injection, call your healthcare provider or go to the nearest hospital emergency room right away.
- You should write down when you have headaches and when you take sumatriptan injection so you can talk with your healthcare provider about how sumatriptan injection is working for you.

What should I avoid while taking sumatriptan injection?

Sumatriptan can cause dizziness, weakness, or drowsiness. If you have these symptoms, do not drive a car, use machinery, or do anything where you need to be alert.

What are the possible side effects of sumatriptan injection?

Sumatriptan may cause serious side effects. See “What is the most important information I should know about sumatriptan injection?”

These serious side effects include:

- changes in color or sensation in your fingers and toes (Raynaud's syndrome)

- stomach and intestinal problems (gastrointestinal and colonic ischemic events). Symptoms of gastrointestinal and colonic ischemic events include:
 - sudden or severe stomach pain
 - stomach pain after meals
 - weight loss
 - nausea or vomiting
 - constipation or diarrhea
 - bloody diarrhea
 - fever
- problems with blood circulation to your legs and feet (peripheral vascular ischemia). Symptoms of peripheral vascular ischemia include:
 - cramping and pain in your legs or hips
 - feeling of heaviness or tightness in your leg muscles
 - burning or aching pain in your feet or toes while resting
 - numbness, tingling, or weakness in your legs
 - cold feeling or color changes in 1 or both legs or feet
- medication overuse headaches. Some people who use too many sumatriptan injections may have worse headaches (medication overuse headache). If your headaches get worse, your healthcare provider may decide to stop your treatment with sumatriptan.
- serotonin syndrome. Serotonin syndrome is a rare but serious problem that can happen in people using sumatriptan injection, especially if sumatriptan injection is used with antidepressant medicines called SSRIs or SNRIs.

Call your healthcare provider right away if you have any of the following symptoms of serotonin syndrome:

- mental changes such as seeing things that are not there (hallucinations), agitation, or coma
 - fast heartbeat
 - changes in blood pressure
 - high body temperature
 - tight muscles
 - trouble walking
- seizures. Seizures have happened in people taking sumatriptan injection who have never had seizures before. Talk with your healthcare provider about your chance of having seizures while you take sumatriptan injection.
- The most common side effects of sumatriptan injection include:
- pain or redness at your injection site
 - tingling or numbness in your fingers or toes
 - dizziness
 - warm, hot, burning feeling to your face (flushing)
 - discomfort or stiffness in your neck
 - feeling weak, drowsy, or tired

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of sumatriptan injection. For more information, ask your healthcare provider or pharmacist.

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

How should I store sumatriptan injection?

- Store at 25°C (77°F); excursions permitted 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].
- Store your medicine away from light.
- Keep your medicine in the packaging or carrying case provided with it.

Keep sumatriptan injection and all medicines out of the reach of children.

General information about the safe and effective use of sumatriptan injection

Medicines are sometimes prescribed for purposes other than those listed in Patient Information leaflets. Do not use sumatriptan injection for a condition for which it was not prescribed. Do not give sumatriptan injection to other people, even if they have the same symptoms you have. It may harm them.

This Patient Information leaflet summarizes the most important information about sumatriptan injection. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about sumatriptan injection that is written for healthcare professionals.

For more information, call 1-888-375-3784.

What are the ingredients in sumatriptan injection?

Active ingredient: sumatriptan succinate USP

Inactive ingredients: sodium chloride, water for injection

The other brands listed are trademarks of their respective owners and are not trademarks of Dr. Reddy's Laboratories Limited. The makers of these brands are not affiliated with and do not endorse Dr. Reddy's Laboratories Limited or its products.

SUMATRIPTAN INJECTION INSTRUCTIONS FOR USE OF DISPOSABLE SUMATRIPTAN AUTOINJECTOR SYSTEM

Read this Patient Instructions for Use before you start to use Sumatriptan Autoinjector System. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or treatment. You and your healthcare provider should talk about sumatriptan injection when you start taking it and at regular checkups.



- Use the device immediately once the cap has been removed; it is advised not to postpone the injection.
- Keep the Sumatriptan Autoinjector System out of the reach of children.

Instructions for Use of Autoinjector Pen

Important things that you need to know

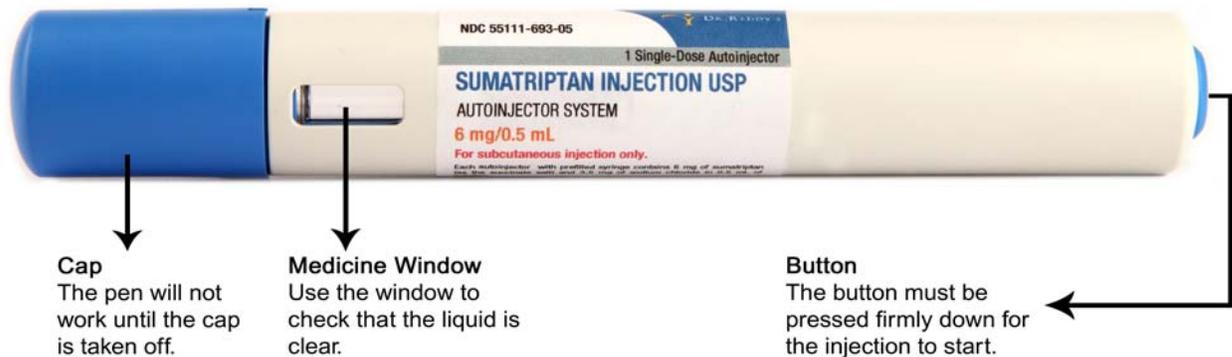
This device is called an Autoinjector pen. Here we use the shorter name ‘pen’.

1. Read all of the instructions carefully before using this pen.
2. Follow these step-by-step instructions every time you use the pen.
3. Only use each pen once - do not try to use more than once.
4. If you have any further questions, ask your doctor or pharmacist. – **Auto**

A. ABOUT THE AUTOINJECTOR PEN

B.

The parts of the pen are shown in this picture.



B. GETTING READY

Getting ready for the injection

1. Wash your hands
2. Choose an area with an adequate fatty tissue layer.
3. Clean the skin area to be injected with alcohol or a new sterile swab

THIGH

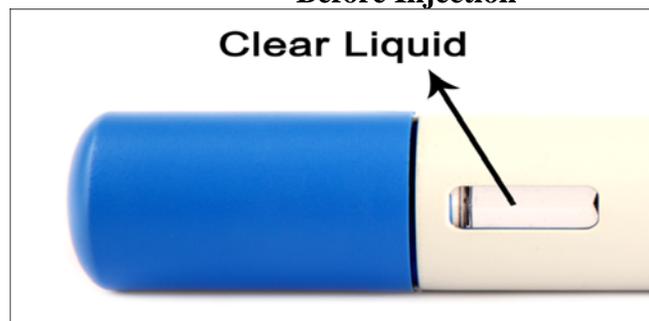
ARM



Getting the pen ready

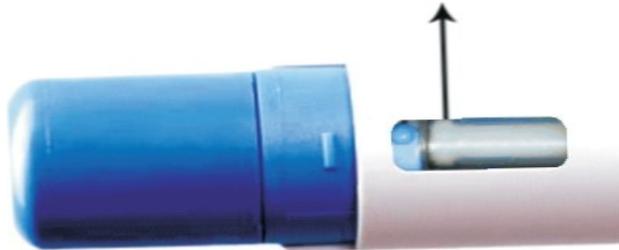
4. Take the pen out of the package
5. Look in the medicine window on the pen
 - Before injection, to check that the liquid is clear.
 - If it is difficult to see what is in the window, hold the pen up to the light and check.
 - After injection, the plunger rod completely fills the medicine window.

Before Injection



After Injection

Plunger rod



If the plunger rod can be seen through the medicine window, the pen is spent and cannot be used again.

6. Pull the cap off the pen

- Do not twist the cap
- Pull it straight off
- Keep the cap for step 14.



7. Look inside the cap, check that the gray needle cover is inside.

- Do not use the pen if the gray needle cover is not inside the cap.



8. Do not try to put the cap back

- If you try to put it back, this will damage the needle.
You are now ready to inject the medicine, go to step 9.

C. INJECTING THE MEDICINE

9. Without pressing the blue button, push the pen firmly against your skin.

- You will now see a small blue circle in the medicine window.
- **As long as the blue circle is visible in the medicine window, the safety lock is de-activated; the pen could fire unintentionally if the blue button is pressed by accident.**



Keep the pen pressed against your skin for the next steps

10. Do not attempt to re-engage the safety lock at any time.

11. Firmly press down the blue button on the top of the pen until it will not go further.

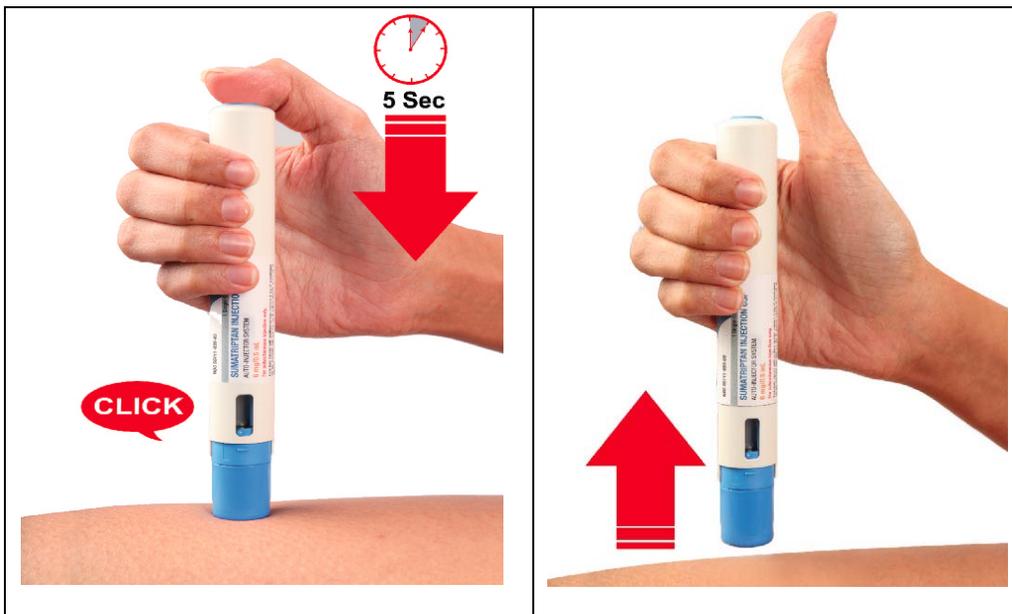
- You will hear a loud click (this indicates that the injection has started)
- Keep pushing the pen against your skin



12. Do not take the pen off your skin

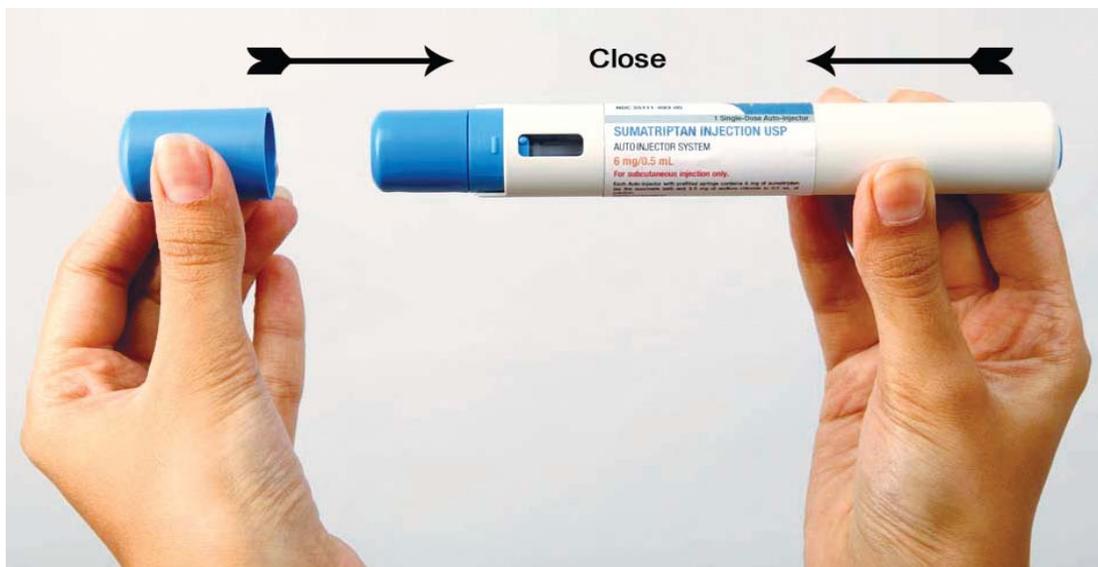
- Wait for about 5 seconds until you hear the second loud click.
 - The second click indicates that the injection has finished.
- If you take the pen off before the second click, not all the medicine will be injected.

13. Carefully take the pen off your skin.



D.WHAT TO DO AFTER THE INJECTION

14. Replace the cap right away



If you notice a spot of blood at the injection site, dab away with a cotton ball or tissue paper. Do not rub the injection site. If needed, you may cover the injection site with a bandage.

**15. Discard the whole sumatriptan injection autoinjector after use.
Do not try to reuse the autoinjector pen**

This Patient Information and Instructions for Use has been approved by the U.S. Food and Drug Administration.

To reorder additional Patient information sheets contact Dr. Reddy's Customer Service at 1-866-733-3952.

Rx Only

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