NOTE: At no time point were the 40 mg once a day pre-operative and the 30 mg every 12 hours postoperative hip replacement surgery prophylactic regimens compared in clinical trials. Injection site hematomas during the extended prophylaxis period after hip replacement surgery occurred in 9% of the Lovenox patients versus 1.8% of the placebo patients.

Table 4: Major Bleeding Episodes in Medical Patients with Severely Restricted Mobility during Acute Illness*

	Dosing Regimen		
Indication	**Lovenox**† 20 mg daily subcutaneously	**Lovenox**† 40 mg daily subcutaneously	**Placebo**†
Medical Patients during Acute Illness	n=351 1 (<1%)	n=360 3 (<1%)	n=362 2 (<1%)

* Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, (2) if the hemorrhage caused a decrease in hemoglobin of ≥2 g/dL or transfusion of 2 or more units of blood products. Retroperitoneal and intracranial hemorrhages were always considered major although none were reported during the trial.

† The rates represent major bleeding on study medication up to 24 hours after last dose.

Table 5: Major Bleeding Episodes in Deep Vein Thrombosis with or without Pulmonary Embolism Treatment*

	Dosing Regimen†		
Indication	**Lovenox** 1.5 mg/kg daily subcutaneously	**Lovenox** 1 mg/kg q12h subcutaneously	**Heparin** aPTT Adjusted Intravenous Therapy
Treatment of DVT and PE	n=298 5 (2%)	n=559 9 (2%)	n=554 9 (2%)

* Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease ≥2 g/dL or transfusion of 2 or more units of blood products. Retroperitoneal, intraocular, and intracranial hemorrhages were always considered major.

† All patients also received warfarin sodium (dose-adjusted according to PT to achieve an INR of 2.0 to 3.0) commencing within 72 hours of Lovenox or standard heparin therapy and continuing for up to 90 days.

Table 6: Major Bleeding Episodes in Unstable Angina and Non–Q-Wave Myocardial Infarction

	Dosing Regimen	
Indication	**Lovenox*** 1 mg/kg q12h subcutaneously	**Heparin*** aPTT Adjusted Intravenous Therapy
Unstable Angina and Non–Q-Wave MI†,‡	n=1578 17 (1%)	n=1529 18 (1%)

* The rates represent major bleeding on study medication up to 12 hours after dose.

† Aspirin therapy was administered concurrently (100 to 325 mg per day).

‡ Bleeding complications were considered major: (1) if the hemorrhage caused a significant clinical event, or (2) if accompanied by a hemoglobin decrease by ≥3 g/dL or transfusion of 2 or more units of

blood products. Intraocular, retroperitoneal, and intracranial hemorrhages were always considered major.

Table 7: Major Bleeding Episodes in Acute ST-Segment Elevation Myocardial Infarction

Indication	Dosing Regimen	
	Lovenox* Initial 30 mg intravenous bolus followed by 1 mg/kg q12h subcutaneously	**Heparin*** aPTT Adjusted Intravenous Therapy
Acute ST-Segment Elevation Myocardial Infarction	n=10176 n (%)	n=10151 n (%)
Major bleeding (including ICH)†	211 (2.1)	138 (1.4)
Intracranial hemorrhages (ICH)	84 (0.8)	66 (0.7)

* The rates represent major bleeding (including ICH) up to 30 days.

† Bleedings were considered major if the hemorrhage caused a significant clinical event associated with a hemoglobin decrease by ≥5 g/dL. ICH were always considered major.

Elevations of Serum Aminotransferases

Asymptomatic increases in aspartate (AST [SGOT]) and alanine (ALT [SGPT]) aminotransferase levels greater than three times the upper limit of normal of the laboratory reference range have been reported in up to 6.1% and 5.9% of patients, respectively, during treatment with Lovenox.

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 Lovenox should be interpreted with caution.

Local Reactions

Local irritation, pain, hematoma, ecchymosis, and erythema may follow subcutaneous injection of Lovenox.

Adverse Reactions in Patients Receiving Lovenox for Prophylaxis or Treatment of DVT, PE

Other adverse reactions that were thought to be possibly or probably related to treatment with Lovenox, heparin, or placebo in clinical trials with patients undergoing hip or knee replacement surgery, abdominal or colorectal surgery, or treatment for DVT and that occurred at a rate of at least 2% in the Lovenox group, are provided below (see Tables 8 to 11).

Table 8: Adverse Reactions Occurring at ≥2% Incidence in Lovenox-Treated Patients Undergoing Abdominal or Colorectal Surgery

	Dosing Regimen			
	Lovenox 40 mg daily subcutaneously n=1228 %		**Heparin** 5000 U q8h subcutaneously n=1234 %	
Adverse Reaction	**Severe**	**Total**	**Severe**	**Total**
Hemorrhage	<1	7	<1	6
Anemia	<1	3	<1	3
Ecchymosis	0	3	0	3

Table 9: Adverse Reactions Occurring at ≥2% Incidence in Lovenox-Treated Patients Undergoing Hip or Knee Replacement Surgery

	Dosing Regimen									
	Lovenox 40 mg daily subcutaneously				**Lovenox** 30 mg q12h subcutaneously		**Heparin** 15,000 U/24h subcutaneously		**Placebo** q12h subcutaneously	
	Peri-operative Period n=288* %		Extended Prophylaxis Period n=131† %		n=1080 %		n=766 %		n=115 %	
Adverse Reaction	**Severe**	**Total**	**Severe**	**Total**	**Severe**	**Total**	**Severe**	**Total**	**Severe**	**Total**
Fever	0	8	0	0	<1	5	<1	4	0	3
Hemorrhage	<1	13	0	5	<1	4	1	4	0	3
Nausea	–	–	–		<1	3	<1	2	0	2
Anemia	0	16	0	<2	<1	2	2	5	<1	7
Edema	–	–	–	–	<1	2	<1	2	0	2
Peripheral edema	0	6	0	0	<1	3	<1	4	0	3

* Data represent Lovenox 40 mg subcutaneously once a day initiated up to 12 hours prior to surgery in 288 hip replacement surgery patients who received Lovenox peri-operatively in an unblinded fashion in one clinical trial.

† Data represent Lovenox 40 mg subcutaneously once a day given in a blinded fashion as extended prophylaxis at the end of the peri-operative period in 131 of the original 288 hip replacement surgery patients for up to 21 days in one clinical trial.

Table 10: Adverse Reactions Occurring at ≥2% Incidence in Lovenox-Treated Medical Patients with Severely Restricted Mobility during Acute Illness

Adverse Reaction	Dosing Regimen	
	Lovenox 40 mg daily subcutaneously n=360 %	**Placebo** daily subcutaneously n=362 %
Dyspnea	3.3	5.2
Thrombocytopenia	2.8	2.8
Confusion	2.2	1.1
Diarrhea	2.2	1.7
Nausea	2.5	1.7

Table 11: Adverse Reactions Occurring at ≥2% Incidence in Lovenox-Treated Patients Undergoing Treatment of Deep Vein Thrombosis with or without Pulmonary Embolism

Adverse Reaction	Dosing Regimen					
	Lovenox 1.5 mg/kg daily subcutaneously n=298 %		**Lovenox** 1 mg/kg q12h subcutaneously n=559 %		**Heparin** aPTT Adjusted Intravenous Therapy n=544 %	
	Severe	**Total**	**Severe**	**Total**	**Severe**	**Total**
Injection Site Hemorrhage	0	5	0	3	<1	<1
Injection Site Pain	0	2	0	2	0	0
Hematuria	0	2	0	<1	<1	2

Adverse Events in Lovenox-Treated Patients with Unstable Angina or Non–Q-Wave Myocardial Infarction

Non-hemorrhagic clinical events reported to be related to Lovenox therapy occurred at an incidence of ≤1%.

Non-major hemorrhagic events, primarily injection site ecchymosis and hematomas, were more frequently reported in patients treated with subcutaneous Lovenox than in patients treated with intravenous heparin.

Serious adverse events with Lovenox or heparin in a clinical trial in patients with unstable angina or non–Q-wave myocardial infarction that occurred at a rate of at least 0.5% in the Lovenox group are provided below (see Table 12).

Table 12: Serious Adverse Events Occurring at ≥0.5% Incidence in Lovenox-Treated Patients with Unstable Angina or Non−Q-Wave Myocardial Infarction

	Dosing Regimen	
	Lovenox 1 mg/kg q12h subcutaneously n=1578	**Heparin** aPTT Adjusted Intravenous Therapy n=1529
Adverse Event	n (%)	n (%)
Atrial fibrillation	11 (0.70)	3 (0.20)
Heart failure	15 (0.95)	11 (0.72)
Lung edema	11 (0.70)	11 (0.72)
Pneumonia	13 (0.82)	9 (0.59)

Adverse Reactions in Lovenox-Treated Patients with Acute ST-Segment Elevation Myocardial Infarction

In a clinical trial in patients with acute ST-segment elevation myocardial infarction, thrombocytopenia occurred at a rate of 1.5%.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of Lovenox. 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.

There have been reports of epidural or spinal hematoma formation with concurrent use of Lovenox and spinal/epidural anesthesia or spinal puncture. The majority of patients had a postoperative indwelling epidural catheter placed for analgesia or received additional drugs affecting hemostasis such as NSAIDs. Many of the epidural or spinal hematomas caused neurologic injury, including long-term or permanent paralysis.

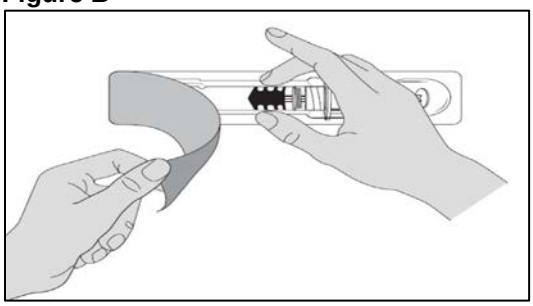
Local reactions at the injection site (e.g. nodules, inflammation, oozing), systemic allergic reactions (e.g. pruritus, urticaria, anaphylactic/anaphylactoid reactions including shock), vesiculobullous rash, cases of hypersensitivity cutaneous vasculitis, purpura, skin necrosis (occurring at either the injection site or distant from the injection site), thrombocytosis, and thrombocytopenia with thrombosis *[see Warnings and Precautions (5.5)]* have been reported.

Cases of hyperkalemia have been reported. Most of these reports occurred in patients who also had conditions that tend toward the development of hyperkalemia (e.g., renal dysfunction, concomitant potassium-sparing drugs, administration of potassium, hematoma in body tissues). Very rare cases of hyperlipidemia have also been reported, with one case of hyperlipidemia, with marked hypertriglyceridemia, reported in a diabetic pregnant woman; causality has not been determined.

Cases of headache, hemorrhagic anemia, eosinophilia, alopecia, hepatocellular and cholestatic liver injury have been reported.

Osteoporosis has also been reported following long-term therapy.

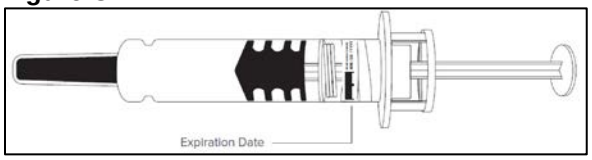
Figure B



Step 4: Check the Lovenox prefilled syringe

- When you receive your Lovenox syringes, always check to see that:
  - you have the correct medicine and dose.
  - the expiration date on the prefilled syringe has not passed (see Figure C).
- **Do not use the Lovenox prefilled syringe if the expiration date has passed.**

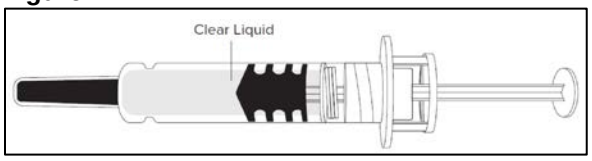
Figure C



Step 5: Check the medicine

- Look at the medicine inside the Lovenox prefilled syringe:
  - The liquid should be clear and colorless to pale yellow (see Figure D).
  - **Note:** You may see air bubble(s), this is normal. Do not try to remove any air bubbles.
- **Do not use the Lovenox prefilled syringe if the liquid is discolored or cloudy, or if it contains visible flakes or particles.**

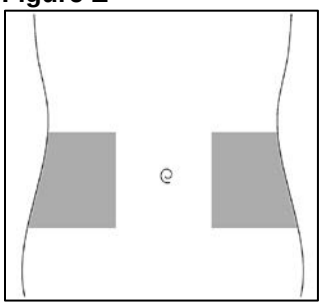
Figure D



Step 6: Choose your injection site

- You can inject into either the right or left side of your stomach area (abdomen), at least 2 inches away from your belly button and out towards your side (see Figure E).
- You should alternate between the left or right side of your stomach each time you give yourself an injection.
- **Do not inject into skin that has bruises or scars.**
- **Do not inject through clothes.**

Figure E

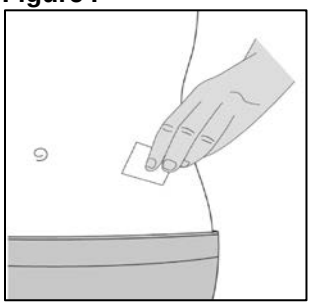


Step 7: Clean the injection site

Clean the injection site with an alcohol wipe (see Figure F).

Let your skin dry before injecting.

Figure F

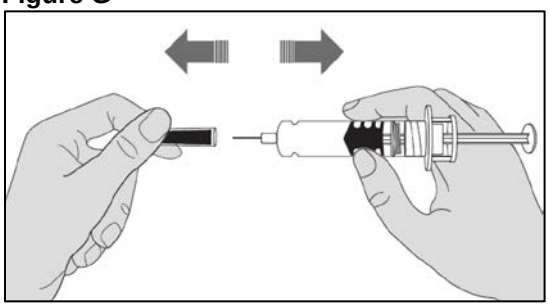


Step 8: Remove the needle cap

Hold the prefilled syringe in the middle of the body with the needle pointing away from you. Remove the needle cap by pulling it straight off the syringe (see Figure G).

- **Do not twist the needle cap to avoid bending the needle.**
- **Do not put the needle cap back on.**
- **Do not touch the needle.**

Figure G

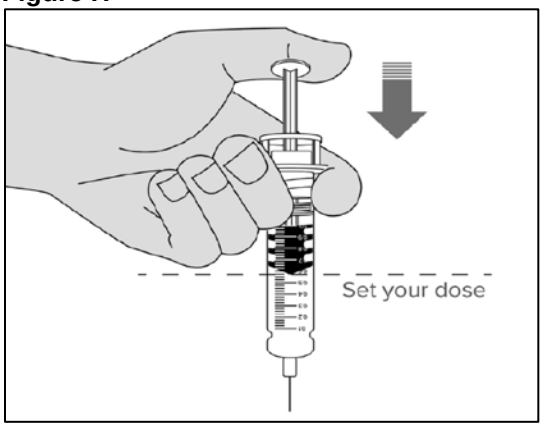


Step 9: Injecting a dose that is less than the full amount in the prefilled syringe. If your prescribed dose is the same as the amount in the prefilled syringe, go to Step 10.

If your dose is based on your bodyweight, your healthcare provider may prescribe less than the full amount in the syringe. You will have to get rid of (discard) some of the medicine from the prefilled syringe before you inject Lovenox.

To measure your prescribed dose, hold the prefilled syringe with the needle pointing down. Carefully watch the numbers on the syringe as you push the plunger down until the amount left in the syringe is the same as your prescribed dose. The tip of the plunger should line up with the number for your prescribed dose (see Figure H).

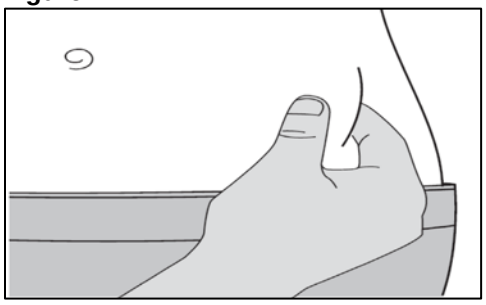
Figure H



Step 10: Injecting Lovenox

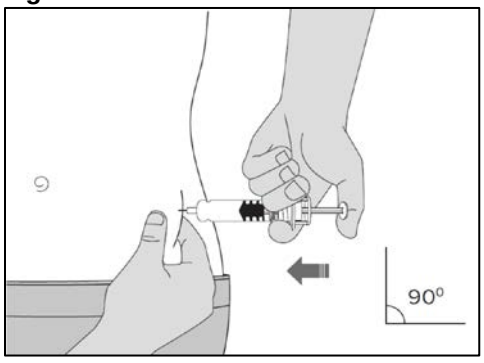
Hold the prefilled syringe like a pencil in your hand with the needle pointing down. With your other hand, pinch the cleaned stomach (abdomen) area between your forefinger and thumb to make a fold in the skin (see Figure I). Make sure you hold the skin fold during the entire injection.

Figure I



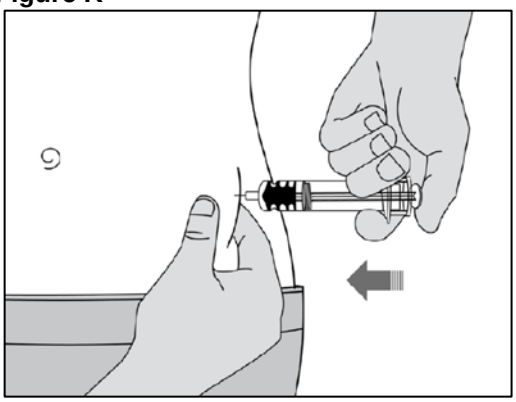
Insert the full length of the needle straight into the skin fold at about a 90° angle (see Figure J).

Figure J



Push the plunger rod down slowly and steadily with your thumb until the Lovenox prefilled syringe is empty (see Figure K).

Figure K

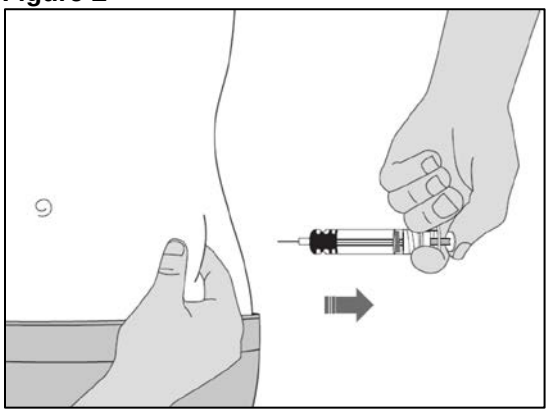


Step 11: Remove the needle

Remove the needle from the injection site by pulling it straight out while keeping your fingers on the plunger rod (see Figure L).

- **Do not put the needle cap back on.**
- **Do not rub your skin after the injection.**

Figure L

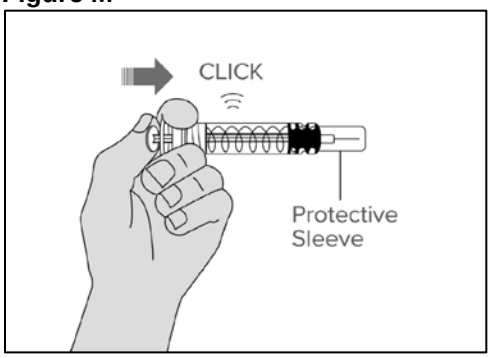


Step 12: Activate the safety system

Point the needle away from yourself and other people, and firmly push the plunger rod again to activate the safety system. The protective sleeve will automatically come down and cover the needle. You will hear a “click” when the protective sleeve is released (see Figure M).

- **You will feel some resistance. This is normal. Keep pushing until you hear the “click.”**
- **The safety system can only be activated after the syringe has been emptied.**
- **Only activate the safety system after you have removed the needle from your skin.**
- **Activation of the safety system may cause a small amount of liquid to leak out of the syringe. Activate the system while facing the syringe away from yourself and other people.**

Figure M



Step 13: Dispose of used Lovenox prefilled syringes and needle caps

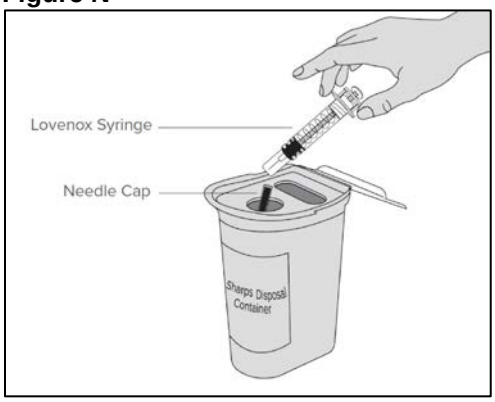
Put the used Lovenox prefilled syringe and needle cap in an FDA-cleared sharps disposal container right away after use (see Figure N). **Do not dispose of Lovenox prefilled syringes or needle caps in your household trash.**

If you do not have an FDA-cleared sharps disposal container, you may use a household container that is:

- made of a heavy-duty plastic,
- can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
- upright and stable during use,
- leak-resistant, and
- properly labeled to warn of hazardous waste inside the container.

When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles, syringes, and prefilled syringes. For more information about safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at http://www.fda.gov/safesharpsdisposal.

Figure N



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This Instructions for Use has been approved by the U.S. Food and Drug Administration.
Issued: December 2021