VENTURA COUNTY HEALTH CARE PLAN

Prior Authorization DRUG Guidelines

LOVENOX (enoxaparin)

Effective Date: 7/28/05

Date Developed: 7/11/05 by C. Wilhelmy MD

Last Approval Date: 1/26/16, 1/24/17, 1/22/19, 2/18/20, 2/2/21, 8/3/21, 2/1/22, 1/31/23, 2/13/24, 2/18/25

(Archived: 1/1/18)

Unarchived Date: 1/22/19 (Formulary Exclusion – For Exception Review Use)

Lovenox is a low-molecular weight (fractionated) form of heparin that has a higher ratio of anti-factor Xa to anti-factor IIa activity and a smaller effect on the activated partial thromboplastin time than unfractionated heparin.

Labeled Uses:

Acute coronary syndromes: Unstable angina, non-ST-elevation myocardial infarction, and ST-elevation myocardial infarction.

Deep vein thrombosis treatment (acute): Inpatient treatment (patients with or without pulmonary embolism [PE]) and outpatient treatment (patients without PE).

Venous thromboembolism prophylaxis: Following hip or knee replacement surgery, abdominal surgery, or in medical patients with severely restricted mobility during acute illness who are at risk for thromboembolic complications.

Off-label Uses:

Frostbite; Hemodialysis, intermittent, anticoagulation of circuit; Mechanical heart valve, bridging anticoagulation; Periprocedural bridging anticoagulation for patients at high risk of thromboembolism, with atrial fibrillation, venous thromboembolism, or other high-risk conditions; Pulmonary embolism, acute; Superficial vein thrombosis, acute symptomatic; Venous thromboembolism prophylaxis, bariatric surgery patients at high risk for venous thromboembolism, perioperative; Venous thromboembolism prophylaxis, nonmajor orthopedic surgery of lower limb; Venous thromboembolism prophylaxis, nonorthopedic surgery and trauma; Venous thromboembolism prophylaxis in patients with multiple myeloma receiving immunomodulatory therapy who are at a higher risk for venous thromboembolism; Venous

thromboembolism prophylaxis, pregnancy

CONTRAINDICATIONS

Known hypersensitivity to enoxaparin (eg, pruritus, urticaria, anaphylactic/anaphylactoid reactions), heparin, pork products, or any component of the formulation (including benzyl alcohol in multiple-dose vials)

History of immune mediated heparin-induced thrombocytopenia (HIT) in the past 100 days or in the presence of circulating antibodies

Active major bleeding (e.g. active gastric or duodenal ulcer; hemorrhagic cerebrovascular accident (except if there are systemic emboli); severe uncontrolled hypertension; diabetic or hemorrhagic retinopathy

Injuries to and operations on the brain, spinal cord, eyes, and ears

WARNINGS

- Lovenox Injection is not intended for intramuscular administration.

- Lovenox Injection cannot be used interchangeably (unit for unit) with heparin or other low molecular weight heparins as they differ in manufacturing process, molecular weight distribution, anti-Xa and anti-IIa activities, units, and dosage. Each of these medicines has its own instructions for use.

- Hemorrhage: Lovenox Injection, like other anticoagulants, should be used with extreme caution in conditions with increased risk of hemorrhage, such as bacterial endocarditis, congenital or acquired bleeding disorders, active ulcerative and angiodysplastic gastrointestinal disease, hemorrhagic stroke, or ophthalmological surgery, or in patients treated concomitantly with platelet inhibitors.

- **US Boxed Warning:** Cases of epidural or spinal hematomas have been reported with the associated use of Lovenox Injection and spinal/epidural anesthesia or spinal puncture resulting in long- term or permanent paralysis. The risk of these events is higher with the use of post- operative indwelling epidural catheters or by the concomitant use of additional drugs affecting hemostasis such as NSAIDs. Major hemorrhages including retroperitoneal and intracranial bleeding have been reported. Some of these cases have been fatal.

- Bleeding can occur at any site during therapy with Lovenox Injection. An unexplained fall in hematocrit or blood pressure should lead to a search for a bleeding site.

- Thrombocytopenia can occur with the administration of Lovenox Injection.

Thrombocytopenia of any degree should be monitored closely. If the platelet count falls below 100,000/mm^3, Lovenox Injection should be discontinued. Cases of heparin-induced thrombocytopenia with thrombosis have also been observed in clinical practice. Some of these cases were complicated by organ infarction, limb ischemia, or death.

Pregnant Women with Mechanical Prosthetic Heart Valves. Women with mechanical prosthetic heart valves may be at higher risk for thromboembolism during pregnancy, and, when pregnant, have a higher rate of fetal loss from stillbirth, spontaneous abortion and premature delivery. Therefore, frequent monitoring of peak and trough anti-Factor Xa levels and adjusting of dosage may be needed.

Miscellaneous: Lovenox multiple-dose vials contain benzyl alcohol as a preservative. The administration of medications containing benzyl alcohol as a preservative to premature neonates has been associated with a fatal "Gasping Syndrome". Because benzyl alcohol may cross the placenta, Lovenox multiple-dose vials, preserved with benzyl alcohol, should be used with caution in pregnant women and only if clearly needed.

PRECAUTIONS

Renal Impairment: In patients with renal impairment, there is an increase in exposure of enoxaparin sodium. All such patients should be observed carefully for signs and symptoms of bleeding. Because exposure of enoxaparin sodium is significantly increased in patients with severe renal impairment (creatinine clearance <30 mL/min), a dosage adjustment is recommended for therapeutic and prophylactic dosage ranges. No dosage adjustment is recommended in patients with moderate (creatinine clearance 30-50 mL/min) and mild (creatinine clearance 50-80 mL/min) renal impairment.

Low-Weight Patients: An increase in exposure of enoxaparin sodium with prophylactic dosages (non-weight adjusted) has been observed in low-weight women (<45 kg) and low-weight men (<57 kg). All such patients should be observed carefully for signs and symptoms of bleeding.

Laboratory Tests: Periodic complete blood counts, including platelet count, and stool occult blood tests are recommended during the course of treatment with Lovenox Injection. When administered at recommended prophylaxis doses, routine coagulation tests such as Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT) are relatively insensitive measures of Lovenox Injection activity and, therefore, unsuitable for monitoring. Anti-Factor Xa may be used to monitor the anticoagulant effect of Lovenox Injection in patients with significant renal impairment. If during Lovenox Injection therapy abnormal coagulation parameters or bleeding should occur, anti-Factor Xa levels may be used to monitor the anticoagulant effects of Lovenox Injection.

Drug Interactions: Unless they are necessary, agents which may enhance the risk of hemorrhage should be discontinued prior to initiation of Lovenox Injection therapy. These agents include medications such as: anticoagulants, platelet inhibitors including acetylsalicylic

acid, salicylates, NSAIDs (including ketorolac tromethamine), dipyridamole, or sulfinpyrazone. If co-administration is essential, conduct close clinical and laboratory monitoring.

Pregnancy (Pregnancy Category B)**:**

Lovenox is not predicted to increase the risk of developmental abnormalities. Lovenox does not cross the placenta, based on human and animal studies, and shows no evidence of teratogenic effects or fetotoxicity.

Pediatric Use: Safety and effectiveness of Lovenox Injection in pediatric patients have not been established.

Geriatric Use The risk of Lovenox Injection-associated bleeding is increased with age.

DOSING (ADULT)

Non-ST-elevation acute coronary syndromes: 1 mg/kg every 12 hours with an appropriate antiplatelet regimen; continue for at least 48 hours, until hospital discharge, or until percutaneous coronary intervention (PCI) is performed

ST-elevation myocardial infarction:

Patients <75 years of age*:* Single IV bolus of 30 mg **plus** 1 mg/kg (maximum: 100 mg for the first 2 doses only) SubQ every 12 hours. The first SubQ dose should be administered with the IV bolus.

Patients ≥75 years of age: **Note:** No IV bolus is administered. SubQ: 0.75 mg/kg (maximum: 75 mg for the first 2 doses only) every 12 hours.

Duration: Therapy may be continued for up to 8 days (minimum of 48 hours when undergoing reperfusion with fibrinolysis) or until revascularization

NOTE: Initial dosing is the same for patients who undergo reperfusion with fibrinolysis or PCI and for patients who do not undergo reperfusion. In patients with STEMI receiving thrombolytics, initiate enoxaparin between 15 minutes before and 30 minutes after fibrinolytic therapy. Use in conjunction with an appropriate antiplatelet regimen

Medical/Surgical patients with acute illness at moderate and high risk for venous thromboembolism:

40 mg SubQ once daily; continue for length of hospital stay or until patient is fully ambulatory and risk of VTE has diminished. Extended prophylaxis beyond acute hospital stay is not routinely recommended

Deep vein thrombosis and/or pulmonary embolism (pulmonary embolism is an off-label use): Inpatient treatment: SubQ: 1 mg/kg every 12 hours (preferred) or 1.5 mg/kg once every 24 hours.

Note: In select low-risk patients, may consider outpatient treatment using 1 mg/kg every 12 hours for the remainder of the course after first dose administered in hospital or urgent care center

Renal Impairment: adjust dosage if CrCL<30 mL/minute (see product literature)
DOSAGE FORMS (Lovenox, Generic)

For injection: 300 mg/3 mL (3 mL)
For SubQ: 30 mg/0.3 mL (0.3 mL); 40 mg/0.4 mL (0.4 mL); 60 mg/0.6 mL (0.6 mL); 80 mg/0.8 mL (0.8 mL); 100 mg/mL (1 mL); 120 mg/0.8 mL (0.8 mL); 150 mg/mL (1 mL)

REFERENCES

1. Antman, EM, Anbe, SC, Alpert, JS, et al. ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction-Executive Summary. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). Circulation 2004; 110:588-636. Available at: http://www.circulationaha.org/cgi/content/full/110/5/588. Last accessed August 26, 2004.

2. Antman, EM, Cohen, M, Radley, D, et al. Assessment of the Treatment Effect of Enoxaparin for Unstable Angina/Non-Q-Wave Myocardial Infarction. TIMI 11B-ESSENCE Meta-analysis. Circulation 1999; 100:1602.

3. Antman, EM, McCabe, CH, Gurfinkel, EP, et al. Enoxaparin Prevents Death and Cardiac Ischemic Events in Unstable Angina/Non-Q-Wave Myocardial Infarction. Results of the Thrombolysis in Myocardial Infarction (TIMI) 11B Trial. Circulation 1999; 100:1593.

4. Braunwald, E, Antman, EM, Beasley, JW, et al. ACC/AHA 2002 Guideline Update for the Management of Patients With Unstable Angina and Non-ST-Segment Elevation Myocardial Infarction - Summary Article: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina). J Am Coll Cardiol 2002; 40(7):1366-74. Available at: http://www.acc.org/clinical/guidelines/unstable/incorporated/index.htm. Accessed May 20, 2003.

5. Cohen, M, Bigonzi, F, Le Louer, V, et al. One Year Follow-Up of the ESSENCE Trial (Enoxaparin Versus Heparin in Unstable Angina and Non-Q Wave Myocardial Infarction). J Am Coll Cardiol 1998; 31:79A.

6. Cohen, M, Demers, C, Gurfinkel, EP, et al. A Comparison of Low-Molecular-Weight Heparin With Unfractionated Heparin for Unstable Coronary Artery Disease. Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events Study Group. N Engl J Med 1997; 337:447.

7. Farooq, V, Hegarty, J, Chandrasekar, T, et al. Serious Adverse Incidents With the Usage of Low Molecular Weight Heparins in Patients With Chronic Kidney Disease. Am J Kidney Dis 2004; 43:531.

8. Fox, KA. Low Molecular Weight Heparin (Enoxaparin) in the Management of Unstable Angina: The ESSENCE Study. Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q wave Coronary Events. Heart 1999; 82(Suppl

1):112.

9. Gerlach, AT, Pickworth, KK, Seth, SK, et al. Enoxaparin and Bleeding Complications: A Review in Patients With and Without Renal Insufficiency. Pharmacotherapy 2000; 20:771.

10. Hirsh, J, Dalen, J, Guyatt, G, et al. The Sixth (2000) ACCP Guidelines for Antithrombotic Therapy for Prevention and Treatment of Thrombosis. American College of Chest Physicians. Chest 2001; 119(1 Suppl):346.

11. Monagle, P, Michelson, AD, Bovill, E, et al. Antithrombotic Therapy in Children. Chest 2001; 119:344S.

12. Montalescot, G, Philippe, F, Ankri, A, et al. Early Increase of von Willebrand Factor Predicts Adverse Outcome in Unstable Coronary Artery Disease: Beneficial Effects of Enoxaparin. French Investigators of the ESSENCE Trial. Circulation 1998; 98:294.

13. Nagge, J, Crowther, M, Hirsh, J. Is Impaired Renal Function a Contraindication to the Use of Low-Molecular Weight Heparin. Arch Intern Med 2002; 162:2605.

14. Polkinghorne, KR, McMahon, LP, Becker, GJ. Pharmacokinetic Studies of Dalteparin (Fragmin), Enoxaparin (Clexane), and Danaparoid Sodium (Orgaran) in Stable Chronic Hemodialysis Patients. Am J Kidney Dis 2002; 40:990.

15. Reach, L, Debure, A, de Groc, F, et al. Anticoagulation With Enoxaparin 0.5 mg/kg in 630 Dialysis Sessions. Haemostasis 1994; 24(Suppl 1):280 [Abstract 281].

16. Simonneau, G, Charbonnier, B, Decousus, H, et al. Subcutaneous Low-Molecular-Weight Heparin Compared With Continuous Intravenous Unfractionated Heparin in the Treatment of Proximal Deep Vein Thrombosis. Arch Intern Med 1993; 153:1541.

17. Von Visger, J, Magee, C. Low Molecular Weight Heparins in Renal Failure. J Nephrol 2003; 16:914.

18. Wallentin, L, Goldstein, P, Armstrong, PW, et al. Efficacy amd Safety of Tenecteplase in Combination With the Low-Molecular-Weight Heparin Enoxaparin or Unfractionated Heparin in the Prehospital Setting: The Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT)-3 PLUS Randomized Trial in Acute Myocardial Infarction. Circulation 2003; 108(2): 135-42.

19. Wong, GC, Giugliano, RP, Antman, EM. Use of Low-Molecular-Weight Heparins in the Management of Acute Coronary Artery Syndromes and Percutaneous Coronary Intervention. JAMA 2003; 289:331.

20. Zed, PJ, Tisdale, JE, Borzak, S. Low-Molecular-Weight Heparins in the Management of Acute Coronary Syndromes. Arch Intern Med 1999; 159:1849.

21. Lovenox prescribing information, Sanofi-Aventis , December 2009.

22. Lovenox (enoxaparin) [prescribing information]. Bridgewater, NJ: Sanofi-Aventis US LLC; May 2020.

23. Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G. Oral anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141(2)(suppl):e44S-e88S. doi:10.1378/chest.11-2292

24. Amsterdam EA, Wenger NK, Brindis RG, et al; American College of Cardiology; American Heart Association Task Force on Practice Guidelines; Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons; American Association for Clinical Chemistry. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [published correction appears in J Am Coll Cardiol. 2014;64(24):2713-2714].

25. Curry MA, LaFollette JA, Alexander BR, Evans KS, Tran RH, Kempton CL. Evaluation of treatment-dose enoxaparin in acutely ill morbidly obese patients at an Academic Medical Center: A randomized clinical trial. Ann Pharmacother. 2019;53(6):567-573. doi:10.1177/1060028018821149

26. Hirsh J, Warkentin TE, Shaughnessy SG, et al, “Heparin and Low-Molecular-Weight Heparin: Mechanisms of Action, Pharmacokinetics, Dosing, Monitoring, Efficacy, and Safety,” Chest, 2001, 119:64S-94S.

27. Kahn SR, Lim W, Dunn AS, et al. Prevention of VTE in nonsurgical patients: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice

guidelines. Chest. 2012;141(2)(suppl):e195S-e226S. doi:10.1378/chest.11-2296

28. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report [published correction appears in Chest. 2016;150(4):988]. Chest. 2016;149(2):315-352.

29. King SB 3rd, Smith SC Jr, Hirshfeld JW JR, et al, "2007 Focused Update of the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: 2007 Writing Group to Review New Evidence and Update the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention, Writing on Behalf of the 2005 Writing Committee," Circulation, 2008, 117(2):261-95

Revision History:
Date Revised: 10/10/11; 3/26/12 by A. Reeves MD
Date Reviewed/No Updates: 1/16/13 by A. Reeves MD
Date Approved by P&T Committee: 7/28/05; 10/25/11, 4/24/12; 1/29/13 Date Reviewed/No Updates: 1/28/14 by C. Sanders MD
Date Approved by P&T Committee: 1/28/14
Date Reviewed/No Updates: 1/13/15 by C. Sanders, MD
Date Approved by P&T Committee: 1/27/15
Date Reviewed/No Updates: 1/26/16 by C. Sanders, MD; R. Sterling, MD
Date Approved by P&T Committee: 1/26/16
Date Reviewed/No Updates: 1/24/17 by C. Sanders, MD; R. Sterling, MD
Date Approved by P&T Committee: 1/24/17
Date Reviewed/No Updates: 1/23/18 by C. Sanders, MD; R. Sterling, MD
Date Approved by P&T Committee: 1/23/18
Date Reviewed/Archived: 1/1/18 by C. Sanders, MD; R. Sterling, MD
Date Approved by P&T Committee: 1/23/18
Date Reviewed/No Updates/Unarchived: 1/22/19 by C. Sanders, MD; R. Sterling, MD
Date Approved by P&T Committee: 1/22/19
Date Reviewed/No Updates: 2/18/20 by H. Taekman, MD; R. Sterling, MD
Date Approved by P&T Committee: 2/18/20
Date Reviewed/No Updates: 2/2/21 by H. Taekman, MD; R. Sterling, MD
Date Approved by P&T Committee: 2/2/21
Date Reviewed/No Updates: 2/1/22 by H. Taekman, MD; R. Sterling, MD
Date Approved by P&T Committee: 2/1/22
Date Reviewed/No Updates: 1/21/23 by H. Taekman, MD; R. Sterling, MD
Date Approved by P&T Committee: 1/31/23
Date Reviewed/No Updates: 2/13/24 by H. Taekman, MD; R. Sterling, MD
Date Approved by P&T Committee: 2/13/24
Date Reviewed/Updated: 2/18/25 by H. Taekman, MD; R. Sterling, MD
Date Approved by P&T Committee: 2/18/25

Revision Date	Content Revised (Yes/No)	Contributors	Review/Revision Notes
1/24/17	No	Catherine Sanders, MD; Robert Sterling, MD	Annual review
1/1/18	No	Catherine Sanders, MD; Robert Sterling, MD	Archived – excluded from the Formulary effective 1/1/18
1/22/19	Yes	Catherine Sanders, MD; Robert Sterling, MD	Unarchived – Formulary Exclusion – For Exception Review Use Only Annual review
2/18/20	Yes	Howard Taekman, MD; Robert Sterling, MD	Annual review
2/2/21	Yes	Howard Taekman, MD; Robert Sterling, MD	Annual review
8/3/21	Yes	Howard Taekman, MD; Robert Sterling, MD	Updated contraindications, dosing and references. Formatting changes.
2/1/22	No	Howard Taekman, MD; Robert Sterling, MD	Annual review
1/31/23	No	Howard Taekman, MD; Robert Sterling, MD	Annual review
2/13/24	No	Howard Taekman, MD; Robert Sterling, MD	Annual review
2/18/25	Yes	Howard Taekman, MD; Robert Sterling, MD	Updated Off Label Uses, contraindications, warnings, precautions and dosing sections