

Class: Low molecular weight heparin (LMWH).

Indications: Prevention and treatment of deep vein thrombosis, pulmonary embolism, †thrombophlebitis migrans, †disseminated intravascular coagulation (DIC).

Contra-indications: Active major bleeding, history of heparin-induced thrombocytopenia with unfractionated heparin, thrombocytopenia with positive anti-platelet antibody test.

Pharmacology

Enoxaparin acts by potentiating the inhibitory effect of antithrombin III on Factor Xa and thrombin. It has a relatively higher ability to potentiate Factor Xa inhibition than to prolong plasma clotting time (APTT) which cannot be used to guide dosage. Anti-factor Xa levels can be measured if necessary, e.g. if a patient is at increased risk of bleeding, but routine monitoring is not generally required because the dose is determined by the patient's weight. In renal impairment excretion of enoxaparin is reduced and increased bleeding can occur. LMWH is as effective as unfractionated heparin for the treatment of deep vein thrombosis and pulmonary embolism and is now the initial treatment of choice.^{1,2} Other advantages include a longer duration of action which allows administration q.d. and possibly a better safety profile, e.g. fewer major hemorrhages.¹⁻⁵ LMWH is the treatment of choice for *chronic* DIC; this commonly presents as recurrent thromboses in both superficial and deep veins which do not respond to **warfarin**. **Tranexamic acid** and **aminocaproic acid** (antifibrinolytic drugs) should not be used in DIC because they increase the risk of end-organ damage from microvascular thromboses. All LMWH is derived from porcine heparin and some patients may need to avoid it because of hypersensitivity, or for religious or cultural reasons. The most appropriate non-porcine alternative is **fondaparinux**.

Bio-availability 100% SC (based on plasma anti-factor Xa activity).

Onset of action 5min IV; 3h SC⁶

Time to peak plasma anti-factor Xa activity 2–6h SC.

Plasma anti-factor Xa activity halflife 2–4.5h IV;^{7,8} 4.5–7h SC.

Duration of action >24h SC.⁵

Cautions

Serious drug interactions: enhanced anticoagulant effect with anticoagulant/antiplatelet drugs, e.g. NSAIDs; reduced anticoagulant effect with antihistamines, cardiac glycosides, **tetracycline** and **ascorbic acid**.

Risk of spinal (intrathecal or epidural) hematoma in patients undergoing spinal puncture or with indwelling spinal catheter, particularly if concurrently receiving a drug which affects hemostasis; monitor for neurological impairment. Increased risk of hemorrhage if underlying bleeding diathesis (e.g. thrombocytopenia), recent cerebral hemorrhage, recent neurological or ophthalmic surgery, uncontrolled hypertension, diabetic or hypertensive retinopathy, subacute bacterial endocarditis, current or past peptic ulcer, severe liver disease. Severe renal impairment: the clearance of enoxaparin is decreased by 65% and dose reduction is required if creatinine

clearance <30ml/min. Specialist guidelines suggest using IV unfractionated heparin instead of LMWH but the evidence is not strong (grade 2C, i.e. not based on RCT).⁹

Undesirable effects

For full list, see manufacturer's PI.

Common (<10%, >1%) pain at the injection site, minor bleeding (generally hematoma or ecchymosis at the injection site), major bleeding in surgical patients and patients being treated for deep vein thrombosis or pulmonary embolism (e.g. retroperitoneal, intracranial or intra-ocular bleeding), thrombocytopenia, anemia, ecchymosis, peripheral edema, reversible increases in transaminases (rarely associated with increased bilirubin levels).

Uncommon (<1%, >0.1%) major bleeding in medical patients receiving prophylactic treatment, hematuria.

Both standard heparin and LMWH can cause thrombocytopenia (platelet count <100 × 10⁹/L). An early (<4 days) mild fall in platelet count is often seen after starting heparin therapy, particularly after surgery. This corrects spontaneously despite the continued use of heparin and is asymptomatic.¹⁰ However, occasionally, an immune heparin-induced thrombocytopenia (HIT) develops associated with heparin-dependent IgG antibodies (see LMWH p.000).^{4,10} Enoxaparin should be stopped immediately if there is a fall in the platelet count >50% and the advice of a hematologist obtained. Anticoagulation should be continued with a hirudin derivative, e.g. **lepirudin**, or a direct thrombin inhibitor, e.g. **argatroban**, even if there is no clinically evident thrombosis (see LMWH, p.000).

Dose and use

All patients should have a baseline platelet count before starting enoxaparin. Subsequent routine monitoring depends on the relative risk of HIT (see LMWH, p.000).¹¹

May cause transient stinging and local bruising. Inject SC; rotate injection sites between left and right anterolateral and left and right posterolateral abdominal wall; introduce the total length of the needle vertically into the thickest part of a skin fold produced by squeezing the skin between the thumb and forefinger. Do not rub the injection site.

In severe renal impairment (creatinine clearance <30ml/min), the dose of enoxaparin should be reduced to a maximum of 30mg SC q.d. (thromboprophylaxis) or 1mg/kg SC q.d. (treatment).

Thromboprophylaxis

Patients with cancer undergoing surgery

- give 40mg SC q.d., starting 2h before surgery
- continue for 2–4 weeks;¹² four weeks is more effective than one week.^{13,14}
- consider additional mechanical measures such as graduated compression stockings or intermittent pneumatic compression.¹²

Patients with cancer who are immobile or confined to bed because of a concurrent acute medical illness

- give 40mg SC q.d. (see LMWH, p.000)
- duration of therapy is generally ≤2 weeks^{15,16}
- if anticoagulation is contra-indicated, use graduated compression stockings instead.¹²

Patients with cancer undertaking long-distance air travel (>6h)

- if a LMWH is deemed necessary (see LMWH, p.000), prescribe three injections (one each for the outward and return journeys, and one spare)
- provide training in the correct administration of the injection (see the information on self-administration included in the patient information leaflet)
- self-administer 40mg SC 2–4h before departure¹²
- if there is a stop over, followed by another long flight, another injection is not necessary unless the second flight is more than 24h after the first.

Treatment

Deep vein thrombosis and pulmonary embolism in patients with cancer: initial treatment

- confirm diagnosis radiologically (ultrasound, venogram, V/Q scan, CT pulmonary angiography)
- give 1mg/kg SC b.d. for at least the first 3–6 months of indefinite anticoagulation.⁹

Deep vein thrombosis and pulmonary embolism in patients with cancer: ongoing treatment

Indefinite anticoagulation should be considered for patients who have a deep vein thrombosis, a sudden and severe pulmonary embolism or a persistent major risk factor such as cancer⁹ (see LMWH, p.000). In patients with cancer, long-term LMWH appears as effective as (possibly more effective than) **warfarin**, with a similar (or reduced) risk of bleeding.^{17,18} **Warfarin** should be reserved for those patients whose cancer is relatively stable. When switching to **warfarin**, LMWH should be continued for 2 days after achieving a therapeutic INR. Patients undergoing anticancer treatments should receive LMWH.

In palliative care, because hemorrhagic complications with **warfarin** occur in nearly 50% (possibly related to drug interactions and hepatic dysfunction), LMWH is preferable. It has been used indefinitely and is acceptable to patients.¹⁹⁻²¹ Generally, indefinite anticoagulation is discontinued only if contra-indications develop, or when the patient reaches the stage when symptom relief alone is appropriate, e.g. in the last few weeks of life.

Some centers use a fixed low-dose regimen, independent of body weight (see **dalteparin**, p.000)

Disseminated intravascular coagulation (DIC)

- confirm the diagnosis (see LMWH, p.000)
- do not use **warfarin** because it is ineffective
- for chronic DIC presenting with recurrent thromboses, give enoxaparin as for treatment of deep vein thrombosis
- for chronic or acute DIC presenting with hemorrhagic manifestations (e.g. ecchymoses and hematomas), seek specialist advice.

Thrombophlebitis migrans

- do not use **warfarin** because it is ineffective
- generally responds rapidly to small doses, e.g. ≤60mg/day
- continue treatment indefinitely²²
- if necessary, titrate dose to maximum allowed according to weight, i.e. 1mg/kg b.d. SC.

Overdose

In emergencies, **protamine sulfate** can be used to reverse the effects of enoxaparin:

- for each 1mg (100units) of enoxaparin, give 1mg of **protamine sulfate** if <8h since the overdose, or 0.5mg if >8h
- give a maximum of 50mg by slow IV injection over 10min
- give a further 0.5mg of **protamine sulfate** per 100units of enoxaparin after 2–4h if APTT still prolonged.

Note: even with high doses of **protamine sulfate**, the anti-Xa activity of enoxaparin is not completely neutralized (maximum reversal ~60%).

Supply

Lovenox® (Aventis)

Injection (single dose syringe for SC injection) 100mg/ml, 0.3ml (30mg) = \$17.69, 0.4ml (40mg) = \$23.00, 0.6ml (60mg) = \$34.98, 0.8ml (80mg) = \$46.59, 1ml (100mg) = \$57.89.

150mg/ml, 0.8ml (120mg) = \$50.89, 1ml (150mg) = \$86.89.

Injection (multiple-dose vial for SC injection) 100mg/ml, 3ml (300mg) = \$192.65 (AWP)

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