

Class: Low molecular weight heparin (LMWH).

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

Contra-indications: Patients at risk of haemorrhage (e.g. bleeding diathesis, thrombocytopenia *except disseminated intravascular coagulation*), peptic ulcer, recent cerebral haemorrhage and severe liver disease, subacute bacterial endocarditis.

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 but routine monitoring is not 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 o.d. and possibly a better safety profile (fewer major haemorrhages and lower mortality in some but not all studies).¹⁻⁵ Heparin 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** (an antifibrinolytic drug) should not be used in DIC because it would increase the risk of end-organ damage from microvascular thromboses.

Bio-availability 91% SC.

Time to peak plasma activity 2.5–4h SC.

Plasma half-life 4–5h 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**.

History of heparin-induced thrombocytopenia (*see below*).

Renal failure, hepatic impairment, increased potential for bleeding (e.g. impaired haemostasis, history of peptic ulcer, recent ischaemic stroke, uncontrolled hypertension, retinopathy, recent neurological or ophthalmological surgery).

Undesirable effects

For full list, see manufacturer's SPC.

Local skin reactions at the injection site (erythema, induration, pruritus) and, rarely, systemic reactions (urticaria, angioedema, anaphylaxis). Abnormal liver function tests have been reported. Osteoporosis (long-term use).

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.⁶ However, occasionally, an immune heparin-induced thrombocytopenia (HIT) develops associated with heparin-dependent IgG antibodies.^{4,6} The antibodies form a complex with platelet factor 4 and bind to the platelet surface, *causing disruption of the platelets and a release of procoagulant material*. It can occur up to 4 weeks after starting heparin and manifests as venous or arterial thrombo-embolism which may be fatal. HIT is less common with prophylactic regimens (low doses) than with therapeutic ones (higher doses) and with LMWH rather than unfractionated heparin. Cross-reactivity is rare. HIT typically develops 5–8 days after starting heparin and, for this reason, some centres check the platelet count at this time (Box 2.A). Enoxaparin should be stopped immediately if there is a dramatic fall in the platelet count (30–50%) and anticoagulation continued with a heparinoid, e.g. **danaparoid** or **lepirudin** instead. HIT is more common in the USA (where more bovine heparin is used) than in the UK (where more porcine heparin is used). The risk in the USA has been put at 3% for unfractionated heparin.⁶

Box 2.A Diagnosis and management of HIT^{4,6}

High clinical suspicion for HIT

Platelet count fall generally of 50% or more, or to below $100 \times 10^9/L$, beginning after 5 days of heparin use.

New thrombotic or thrombo-embolic event.

Necrosis or erythematous plaques at injection sites.

Laboratory confirmation

Do one of the following tests but if negative or borderline, do both.

Functional assay for antibodies using washed platelets or citrated platelet-rich plasmas.

Antigen assay (platelet factor 4/heparin ELISA).

Therapeutic approach

Stop heparin or LMWH.

Start treatment with danaparoid or lepirudin.

Do *not* use warfarin alone in acute HIT because this may increase the risk of venous limb gangrene. Warfarin should be given only when the patient is fully anticoagulated with danaparoid or lepirudin. Allow the thrombocytopenia to resolve before continuing with warfarin alone.

Do *not* give prophylactic platelet transfusions.

Dose and use

Inject SC; alternate 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.

Thromboprophylaxis for surgical patients

- give 20mg SC 2h before surgery and o.d. for 7–10 days
- use 40mg SC 12h before surgery and o.d. for 7–10 days in high-risk patients.

Thromboprophylaxis for medical patients

- 40mg SC o.d. for 6–14 days.

Deep vein thrombosis and pulmonary embolism treatment

- confirm diagnosis radiologically (ultrasound, venogram, V/Q scan)
- give 1.5mg/kg SC o.d.
- in patients whose cancer is relatively stable, **warfarin** should be commenced at the same time and LMWH continued for 2 days after achieving a therapeutic INR.

In patients with cancer undergoing treatment, LMWH appears as effective (possibly moreso) than **warfarin**, with a similar (or reduced) risk of bleeding.^{7,8}

In patients with cancer in a palliative care setting, because haemorrhagic complications with **warfarin** occur in nearly 50% (possibly related to drug interactions and hepatic dysfunction), LMWH has been used alone for 4–8 weeks or indefinitely when the risk of recurrence is high.^{9,10}

Disseminated intravascular coagulation (DIC)

- confirm the diagnosis
 - thrombocytopenia (platelet count $<150\,000 \times 10^9/L$ in 95% of cases)
 - decreased plasma fibrinogen concentration
 - elevated plasma D-dimer concentration, a fibrin degradation product (85% of cases)
 - prolonged prothrombin time and/or partial thromboplastin time.¹¹

A normal plasma fibrinogen concentration (200–250mg/100ml) is also suspicious because fibrinogen levels are generally raised in cancer (e.g. 450–500mg/100ml) unless there is extensive liver disease. Infection and cancer both may be associated with an increased platelet count which likewise may mask an evolving thrombocytopenia.

- for *chronic* DIC presenting with recurrent thromboses, give enoxaparin as for treatment of deep vein thrombosis
- for *chronic* or *acute* DIC presenting with haemorrhagic manifestations (e.g. ecchymoses and haematomas), seek specialist advice
- *do not use warfarin because it is ineffective.*

Thrombophlebitis migrans

- generally responds rapidly to small doses, e.g. $\leq 60\text{mg/day}$; continue treatment indefinitely¹²
- titrate dose if necessary to maximum allowed according to weight, i.e. 1.5mg/kg SC daily
- *do not use warfarin because it is ineffective.*

Overdose

- In emergencies, 1mg of **protamine sulfate** can be used to reverse the effects of 1mg enoxaparin; maximum dose 50mg by slow IV injection over 10min. However, even with high doses of protamine, the anti-Xa activity of enoxaparin is never completely neutralised (maximum about 60%).

Supply

Clexane® (Aventis 01732 584 000)

Injection (single dose syringe for subcutaneous injection)

100mg/ml, 0.2ml (20mg) = £3.39, 0.4ml (40mg) = £4.52, 0.6ml (60mg) = £5.11,

0.8ml (80mg) = £5.81, 1ml (100mg) = £7.19.

150mg/ml, 0.8ml (120mg) = £10.51, 1ml (150mg) = £11.94.

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