Enoxaparin Injection (*Clexane* ®)

SCG: For patients undergoing invasive procedures to establish a diagnosis of pulmonary hypertension, assess treatment response or in preparation for surgery

AREAS OF RESPONSIBILITY FOR THE SHARING OF CARE

Introduction:

Pulmonary Arterial Hypertension (PAH) is a disease of the small pulmonary arteries that is characterised by vascular wall thickening (proliferation of media and intima), in-situ thrombus, and as a consequence of these, vascular remodelling. It results in a progressive increase in pulmonary vascular resistance and, ultimately, right ventricular failure and death.

Long term anticoagulation is used in chronic thromboembolic pulmonary hypertension (CTEPH) to prevent recurrent thromboembolism and has also been shown to have a favourable impact in other PAH subgroups

In patients suspected of having pulmonary hypertension, right heart catheterisation is required to confirm the presence of PAH and to establish the specific diagnosis and severity of the disease. Right heart catheterisation may also be required in patients already diagnosed with PAH to assess response to treatment.

In order to reduce the risk of excessive bleeding during catheterisation and other invasive procedures, oral anticoagulation is stopped for several days prior to the procedure. Enoxaparin is then used to prevent venous thromboembolism while the patient's INR is subtherapeutic. Using a low-molecular weight heparin such as enoxaparin is advantageous as it allows the clinician to adequately protect the patient from thromboembolism without introducing unnecessary risk of excessive bleeding during the invasive procedure.

RESPONSIBILITIES and ROLES

General Practitioners responsibilities:

1. Weigh patient and check renal function
2. Prescribe enoxaparin at the recommended dose for the length of time requested by Papworth Hospital (see dosing advice below)
3. Arrange administration of enoxaparin if patient unable/ untrained to self-administer
4. Communicate any adverse events or other problems with the medicine to the supervising consultant at Papworth Hospital
5. Notify hospital specialist if the patient has significant renal impairment
6. Prescribe further enoxaparin post-discharge from hospital if patient's INR < 2 at first community INR check (note: this is usually only required rarely)

Hospital Specialist responsibilities:

Prior to procedure:

1. Send patient-specific instructions on prescribing enoxaparin to the patient's general practitioner (a copy of which goes to the patient)
2. Be available to the general practitioner for advice.
3. Ensure patient and GP are aware when to stop warfarin prior to procedure.
4. Supply (and administer) patient with enoxaparin during the patient's stay in hospital.

After procedure:

5. Restart warfarin (usually this involves reloading)
6. Monitor patient's INR prior to discharge from hospital.
7. Arrange for patients first INR check after discharge from hospital.
8. On discharge, if patient's INR is <2, supply patient with sufficient enoxaparin injection until their next INR check in their local community. (Usually this supply is for 3 – 5 days)
9. Assess and train patient to self administer enoxaparin injection subcutaneously if competent to do so
10. Arrange administration of enoxaparin if patient unable/ untrained to self-administer
11. Ensure the patient is aware of the required dosage of warfarin to take until their INR is next measured in their local community.

Patients Role:

1. Stop taking warfarin as instructed, prior to the procedure
2. Watch for signs of excessive bleeding
3. Inform GP/Hospital of any adverse events
4. Self administer enoxaparin each day as prescribed, if able to do so
5. Recommence warfarin as per hospital instructions and attend anticoagulation clinic and/or GP surgery for INR monitoring

BACK-UP ADVICE AND SUPPORT

Papworth Hospital Main Switchboard	01480 830541
Dr Joanna Pepke-Zaba	ext 4230 or pager 047
Dr Karen Sheares	ext 4757 or pager 841
Pulmonary Vascular Disease Unit Nurses Office	ext 4826 or pager 343
Pharmacy Medicines Information Service (Medical staff only)	01480 364179 (directline) (Mon-Fri 9am-5pm)
Pharmacy Medicines Helpline (answerphone) (Patients only)	01480 364739 (Mon-Fri 9am-5pm)

SUPPORTING INFORMATION

Licensed indication:

- The prophylaxis of thromboembolic disorders of venous origin
- The treatment of venous thromboembolic disease presenting with deep vein thrombosis, pulmonary embolism or both.

Dosage and Administration:

The dosage used for PAH patients at Papworth Hospital is the same as that used for the treatment of venous thromboembolism:

Enoxaparin should be administered once daily as a subcutaneous injection of 1.5mg/kg. (See dosing chart (appendix1). Patients with severe renal impairment (creatinine clearance* < 30ml/minute or in patients undergoing any type of dialysis) should be dosed at 1mg/kg once daily.

Note: Dose is determined by actual body weight. No dosage adjustments are recommended for obesity or low body weight.

It is preferred that the daily injection is administered at approximately 1800hrs so as to coincide with the time the patient would usually take their warfarin.

*(Estimated GFR (eGFR) can be used in place of creatinine clearance in patients of average weight. For advice on assessing renal function for patients at extremes of weight using either eGFR or the Cockroft-Gault equation please contact pharmacy during working hours (see “Back-Up Advice and Support” for contact details)

Contraindications and warnings:

Enoxaparin is contraindicated in patients with acute bacterial endocarditis; major bleeding disorders; thrombocytopenia in patients with a positive in-vitro aggregation test in the presence of enoxaparin; active gastric or duodenal ulceration; hypersensitivity to enoxaparin, other Low Molecular Weight Heparins or heparin; patients receiving heparin for treatment rather than prophylaxis, patients with a high risk of uncontrolled haemorrhage (including recent haemorrhagic stroke).

Use with caution in patients with a history of heparin-induced thrombocytopenia with or without thrombosis. Regular monitoring of platelet count is recommended.

Enoxaparin injection should also be used with caution in conditions with increased potential for bleeding, such as: impaired haemostasis, history of peptic ulcer, recent ischaemic stroke, diabetic retinopathy and recent neuro- or ophthalmologic surgery.

Pregnancy: Animal studies have not shown any teratogenicity, and human studies show that enoxaparin does not cross the placenta during the second trimester (no information is available concerning the first and third trimesters). However, as there are no adequately powered, well-controlled studies in pregnant women this drug should only be used if the physician has established a clear need.

Lactation: It is not known whether unchanged enoxaparin is excreted in human breast milk. The oral absorption of enoxaparin is unlikely. However, as a precaution the manufacturers recommend that lactating mothers receiving enoxaparin should be advised to avoid breast-feeding.

Therapeutic Use:

Enoxaparin is used in patients with CTEPH and some patients with other sub-categories of pulmonary hypertension to decrease their risk of thromboembolism whilst not taking warfarin prior to invasive procedures.

Side Effects:

The most common side effects are

- Excessive bleeding
- Thrombocytopenia (usually mild, transient and asymptomatic)
- Local pain, irritation, haematoma at injection site

Also reported rarely are:

- Skin necrosis
- Cutaneous or systemic allergic reactions
- Increases in liver enzyme levels (reversible)
- Increases in platelet counts (reversible on discontinuation)
- Immuno-allergic thrombocytopenia (see below)

Antibody-mediated heparin-induced thrombocytopenia, should it occur, usually appears between the 5th and the 21st day following the beginning of therapy. If a confirmed significant decrease of the platelet count is observed (30 to 50 % of the initial value), enoxaparin sodium treatment must be immediately discontinued and the patient switched to another therapy.

Heparin products can cause hypoaldosteronism, which may result in an increase in plasma potassium. In rare cases, clinically significant hyperkalaemia may occur in patients with chronic renal failure, diabetes mellitus, pre-existing metabolic acidosis, a raised plasma potassium or those patients taking potassium sparing diuretics. The hyperkaleamia is reversible and appears to be associated with extended heparin treatment beyond 7 days.

Long term treatment with heparin has been associated with a risk of osteoporosis. Although this has not been observed with enoxaparin the risk of osteoporosis cannot be excluded.

Monitoring:

- Confirm body weight and check renal function prior to commencing therapy
- Monitor for signs of excessive bleeding: for example, spontaneous bruising, nose bleeds and bleeding gums.
- Check serum potassium, platelet count and liver enzyme levels after more than 5 days of therapy.

Drug Interactions:

It is recommended by the manufacturers that agents which affect haemostasis should be discontinued prior to enoxaparin therapy unless their use is essential, such as: systemic salicylates, aspirin, NSAIDs, systemic glucocorticoids, thrombolytics and anticoagulants such as warfarin, phenindione, dipyridamole, clopidogrel and drugs with antiplatelet properties such as SSRIs. If the combination cannot be avoided, enoxaparin should be used with careful clinical and laboratory monitoring.

Availability and Cost:

Available from Sanofi-Aventis as 20mg, 40mg, 60mg, 80mg, 100mg, 120mg and 150mg strength prefilled syringes in packs of 10.

Enoxaparin graduated, pre-filled syringes are single dose containers. Discard any unused product.

Community pharmacies can obtain enoxaparin from their wholesalers within 24 hours of issuing an order**.**

Prices per dose range from £4.57 for 60mg up to £11.10 for 150mg. (Prices are taken from BNF No. 59 March 2010)

References:

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- British National Formulary no. 59, London, March 2010
- Schaefer, C, Peters P, and Miller R (eds). Drugs during pregnancy and lactation. 2nd edition. Academic Press. London. 2007
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Appendix 1.

Enoxaparin Dosing Guidelines for Pulmonary Hypertension Patients

Dosage: 1.5 mg / kg bodyweight, once daily

Body weight (kg)	Prescribed dose (rounded)	Injection volume of subcutaneous inj (ml)	Syringe to use	Strength
40 – 42	60 mg	0.60	**60 mg**	100 iu/ml
43 – 44	65 mg	0.65	**80 mg**	100 iu/ml
45 – 47	70 mg	0.70	**80 mg**	
48 – 51	75 mg	0.75	**80 mg**	
52 – 54	80 mg	0.80	**80 mg**	
55 – 57	85 mg	0.85	**100 mg**	100 iu/ml
58 – 61	90 mg	0.90	**100 mg**	
62 – 64	95 mg	0.95	**100 mg**	
65 – 67	100 mg	1.00	**100 mg**	
68 – 72	105 mg	0.70	**120 mg**	150 iu/ml
73 – 76	112.5 mg	0.75	**120 mg**	
77 – 82	120 mg	0.80	**120 mg**	
83 – 86	127.5 mg	0.85	**150 mg**	150 iu/ml
87 – 92	135 mg	0.90	**150 mg**	
93 – 96	142.5 mg	0.95	**150 mg**	
97 – 103	150 mg	1.00	**150 mg**	
104 +	1.5mg/kg rounded to nearest 10mg		**Multiple syringes required per dose**	

Note: This table is for dosing at 1.5mg / kg ONLY. Patients with severe renal impairment (creatinine clearance < 30ml/minute) should be dosed at 1mg / kg once daily.

Administration:
Enoxaparin should be given by deep subcutaneous injection into the lower abdomen when the patient is lying down. The whole length of the needle should be introduced vertically into the skin fold held between the thumb and index finger. Do not release the skin fold until you have withdrawn the needle to minimise irritation to the patient. Do not rub the injection site after administration. Use a different injection site every day and do not inject near any bruising.