Enoxaparin sodium

for long term anticoagulation in patients unsuitable for oral anticoagulants

Prescribe by brand name

(Arovi®▼, Inhixa®, Clexane®)

Traffic light classification: AMBER 2
Information sheet for Primary Care Prescribers

Enoxaparin sodium is the LMWH of choice in Nottinghamshire. Enoxaparin is a biological medicine and as biosimilars are now available and to avoid inadvertent switching, it should be **prescribed by brand name**.

The current brands of choice (based on cost effectiveness) in Nottinghamshire for NEW patients are **Arovi®** (NUH and primary care) and **Inhixa®** (SFH and NHFT).

Key Prescribing Information:

- Prescribe by brand name, NEVER prescribe generically – Clexane® has a different injection device and technique to Arovi® and Inhixa® and is not interchangeable. The colours on the packaging and syringes differ between all three brands.
- Arovi® and Inhixa® share the same injection technique and could be interchanged, if necessary, as long as the patient is informed to prevent any confusion.
- Arovi® is the preferred brand for NEW patients in NUH and in primary care.
- Inhixa® will continue to be the preferred brand at SFH and NHFT.
- Existing patients should ideally continue with the brand they were initiated on.
- There may be patients who have historically been prescribed and continue to use Clexane®. New patients SHOULD NOT be initiated on Clexane®.

Relevant Indications

- Treatment of confirmed or suspected deep vein thrombosis (DVT) and pulmonary embolism (PE), excluding PE likely to require thrombolytic therapy or surgery.
- Treatment of superficial venous thrombosis (SVT) (off label but established practice).
- Prophylaxis of venous thromboembolic disease in pregnancy and the puerperium (off label but established practice).
- Adjunct therapy for high risk coumarin-anticoagulated patients with subtherapeutic INRs.

Therapeutic Summary

Most patients with suspected venous thromboembolic disease are anticoagulated with a Low Molecular Weight Heparin (LMWH) whilst the diagnosis is established, and then proceed to anticoagulation with a direct oral anticoagulant (DOAC) or warfarin. If these agents are unsuitable, the LMWH will be continued long term.

Potential indications for continued treatment with enoxaparin are:

- Liver disease.
- Pregnancy (or patients attempting to conceive as warfarin is potentially teratogenic in the first trimester).

- Anticoagulation in malignancy - patients newly diagnosed with malignancy should not be warfarinised until their treatment plan is agreed, as warfarin control is often very unstable in these patients. Patients with chronic malignant conditions, e.g., prostate cancer, may be suitable for warfarin, but treatment should be reviewed by the specialist team if liver metastases are or become present. For the treatment of VTE in malignancy DOACs or enoxaparin may be used, but each patient is reviewed individually, and any treatment will be decided by the specialist team.
- Recurrent thrombosis despite anticoagulation with coumarin or DOAC.

Medicine Initiation:
Enoxaparin will be initiated in secondary care and the hospital will provide a minimum of 14 days treatment and training on discharge. Patients receiving enoxaparin should also be supplied with sharps boxes.

If discharge is within 14 days from the start of therapy, the GP and patient should be advised of the monitoring requirements to be undertaken. Also see information given to patient's section below.

Dosage and route of administration:
Enoxaparin should be **prescribed by brand name** to avoid inadvertent switching between the multiple biosimilars available in the UK.

Enoxaparin is given by subcutaneous injection, with the dose and frequency determined by indication, the patient's weight, and renal function (see table 1 for adults excluding pregnancy. For dosing in pregnancy - see separate section below).

Some of the doses and frequencies are off label and differ from the SPC:
The licensed treatment dose of enoxaparin changed to harmonise the product licence across Europe. However, some of these changes have not been adopted in the UK and the doses used locally by the acute trusts continue to be those used previously.

Timing of dose:
Enoxaparin should be administered at approximately the same time each day. 6pm has been traditional, but if anti-factor Xa levels are required (very infrequently required and normally only on the advice of a specialist), 8am is preferred as blood samples are required 4 hours post dose.

It is appreciated that in some circumstances, administration at the same time each day is not possible, or that there may be a need to move the time of administration to a more convenient time of day. When moving times of administration, this should be done gradually over a period of a few days. The manufacturer of enoxaparin is unable to offer guidance on appropriate minimum time intervals between doses so prescribers should exercise clinical judgement. It is considered acceptable practice to allow a time window of approximately 2 hours either side of the scheduled time for administration.

Table 1: **Adult recommended enoxaparin subcutaneous doses and frequencies, excluding pregnancy, according to indication, bodyweight, and renal function:**

Indication	Renal function	Weight			
		<50kg	**50-100kg**	**100-150kg**	**>150kg**
Thromboprophylaxis	CrCl ≥30mL/min	20mg once daily	40mg once daily	40mg twice a day	60mg twice a day
	CrCl 15-30mL/min	20mg once daily	20mg once daily	40mg once daily	60mg once daily
	CrCl <15mL/min	20mg once daily[1]			
[1]This is considered generally safe in this patient group but consider seeking senior/specialist advice if used for prolonged periods and/or the patient is at extremes of weight (anti-Xa monitoring can be considered).					
DVT or PE treatment	CrCl ≥30mL/min	1.5mg/kg once daily		NUH: 1.5mg/kg once a day	NUH: 1mg/kg twice a day
				SFH: 1mg/kg twice a day	SFH: 150mg twice a day
	CrCl 15-30mL/min	1mg/kg once daily			
	CrCl <15mL/min	Seek specialist advice			
Mechanical Heart Valves if INR low[2]	CrCl ≥30mL/min	1mg/kg twice a day			
	CrCl 15-30mL/min	1mg/kg once daily			
	CrCl <15mL/min	Seek specialist advice			
[2]Mechanical heart valves if INR <1.8 (unless INR range 1.5-2.5 then if <1.5) and continue until INR at least >2					

DVT or PE treatment in obese patients:

The manufacturer does not give any advice on dosing in obese patients, however local practice is as follows:

- At SFH, a dose of 1mg/kg s/c twice a day is given (up to a maximum of 150mg twice a day) if patients are greater than 100kg.
- At NUH, a dose of 1mg/kg s/c twice a day is given if patients are greater than 150kg.

Pregnancy:

In pregnancy, treatment doses should be based on the patient's early pregnancy weight. Enoxaparin is renally excreted and specific advice should be sought if the woman has renal impairment.

NUH patients are treated with a dose of 1mg/kg s/c twice a day (see table 2).

Table 2: Initial DVT/PE **treatment doses (dose banded)** in pregnancy (NUH):

Early pregnancy weight	Dose of subcutaneous enoxaparin for VTE treatment in pregnancy
<50kg	40mg twice a day
50 – 69kg	60mg twice a day
70 – 89kg	80mg twice a day
90 – 109kg	100mg twice a day
110 – 125kg	120mg twice a day
More than 125kg	Discuss with haematologist

SFH patients are treated with a once-a-day dosing in line with the Trust guidance on treatment of VTE (see table 3).

Table 3: Initial DVT/PE **treatment doses (dose banded)** in pregnancy (SFHT):

Early pregnancy weight	Dose of subcutaneous enoxaparin for VTE treatment in pregnancy
<46kg	60mg once daily
47 – 59kg	80mg once daily
60 – 73kg	100mg once daily
74 – 89kg	120mg once daily
90 – 110kg	150mg once daily
111 – 130kg	120mg **twice a day**
More than 130kg	150mg **twice a day**

Smaller doses are used as **thromboprophylaxis** in high-risk patients (see table 4).

Table 4: Dose of enoxaparin for **thromboprophylaxis** in pregnancy (NUH and SFHT):

Weight	Dose of subcutaneous enoxaparin for thromboprophylaxis in pregnancy
<50kg	20mg once daily
50 – 90kg	40mg once daily
91 – 130kg	60mg once daily
131 – 170kg	80mg once daily
More than 170 kg	0.6 mg/kg/day

If the woman has renal impairment, the dose of enoxaparin may need to be reduced; seek expert advice.

Duration of treatment:
The duration of treatment will depend on the indication for enoxaparin and individual patient factors. The intended duration of therapy will be advised by secondary care on discharge. Patients diagnosed with DVT or PE at NUH will be reviewed at a thrombosis multidisciplinary team meeting, and duration of therapy communicated to the GP. It is acceptable for the GP to stop therapy once the treatment course has been completed without re-referral to secondary care.

Contraindications:

- Acute bacterial endocarditis (risk of haemorrhagic transformation of cerebral emboli).

- Active major bleeding and conditions with a high risk of uncontrolled haemorrhage, including recent haemorrhagic stroke.
- A history of Heparin Induced Thrombocytopenia and Thrombosis (HITT).
- Active gastric or duodenal ulceration.
- Creatinine Clearance <15ml/min.
- Allergy to enoxaparin sodium, heparin or its derivatives including other LMWH.

Precautions:

- Increased potential risk for bleeding:
  - impaired haemostasis including thrombocytopaenia (usually considered safe to give if platelets>50),
  - history of peptic ulcer,
  - recent ischaemic stroke (usually considered safe to give 1 month after the stroke),
  - uncontrolled severe hypertension (systolic BP> 200mmHg, diastolic BP> 100 mmHg),
  - diabetic retinopathy,
  - recent neuro- or ophthalmic surgery.
- As for any patient receiving anticoagulant therapy, in the event of any trauma (especially to the head), referral to the Emergency Department (ED) should be considered.
- LMWHs are derived from pigs so enoxaparin may not be acceptable to some patient groups. A suitable alternative may be fondaparinux, but as a red medication, prescribing responsibility must remain with secondary care.

Adverse Effects:

Haemorrhage:

- Most commonly bruising at the injection site. Ensure that enoxaparin is given by deep subcutaneous injection.
- Refer patient immediately to the ED if serious bleeding occurs e.g., GI bleeding, epistaxis lasting more than 1 hour.

Heparin induced Thrombocytopenia/ Thrombosis (HITT):

- Occurs in <1% of LMWH patients.
- An antibody mediated reaction that usually appears between the 5th and the 15th day following LMWH initiation.
- Regular platelet monitoring is required (see monitoring requirements).

Hyperkalaemia:

- Occurs in <0.1% of patients.
- Due to suppression of adrenal secretion of aldosterone.
- Occurs more commonly in patients with diabetes mellitus, chronic renal failure, pre-existing metabolic acidosis, a raised plasma potassium level prior to treatment or patients taking potassium sparing medicines.
- The risk of hyperkalaemia appears to increase with duration of therapy but is usually reversible on treatment discontinuation.
- Regular electrolyte monitoring required (see monitoring requirements).

Hepatic side effects:

- Transient elevation of liver transaminases may be seen. This is usually reversible on discontinuation.

Osteoporosis:

- Osteoporosis has been reported rarely with long term treatment of enoxaparin (>3months).

Clinically relevant medicine interactions and their management:
Agents which affect haemostasis (e.g., NSAIDS, antiplatelets) should be reviewed and consideration given to their discontinuation prior to enoxaparin therapy. If the combination cannot be avoided, enoxaparin should be used with careful monitoring. Treatment with more than one anticoagulant should only be for the purposes of switching or bridging therapy as part of a clear management plan.

Monitoring requirements:

Frequency of monitoring	Tests to be done	
	Renal function and electrolytes*	FBC
Day 7	✓	✓
Day 14	✓	✓

* Longer term renal function monitoring should be carried out as the patient would usually be monitored i.e., in line with NICE guidance on Chronic Kidney Disease or as indicated in patients with renal pathology.
Monitoring requirements for primary care will be advised on discharge paperwork.

Criteria for review and discontinuation of the medicine:

Side Effect	Action
Platelet count reduction >50% from baseline	Seek immediate haematologist advice (possible HITT).
Haemorrhage	Refer patient immediately to ED if serious bleeding occurs e.g., GI bleeding, epistaxis lasting more than 1 hour.
Excessive bruising (e.g. bruises larger than a palm or purpura on the palate)	Seek immediate haematologist advice.
Significant reduction in renal function	Non-pregnant patients on treatment doses should reduce dose and frequency to 1mg/kg once daily if calculated Creatinine Clearance < 30mL/min (see below). If renal function continues to worsen discuss with haematologist. For pregnant patients, seek advice from the specialist team
Hyperkalaemia	Discuss with haematologist.

eGFR may be considered roughly equivalent to Creatinine Clearance (CrCl), but if the patient is elderly, or if the eGFR is borderline, the CrCl should be calculated using the Cockroft and Gault equation for Creatinine Clearance (mL/min):

$$\text{CrCl} = \frac{(140 - \text{age}) \times \text{weight (kg)}}{\text{serum creatinine (micromol/L)}} \times 1.04 \text{ (female) or } 1.23 \text{ (male)}$$

Information given to patients:
Patients should be counselled on the risks and benefits of their treatment where appropriate. The patient should be told the indication for enoxaparin, intended duration, advised of what side effects to look out for and trained on how to administer the medication.
Patients receiving enoxaparin must be supplied with sharps boxes. The responsibility for providing sharps bins rests with the prescriber that prescribes enoxaparin.

Availability (other biosimilars may also be available)**:**
Enoxaparin should be prescribed by **brand name** and is available as:

- Arovi®▼ pre-filled syringes (100mg/ml or 150mg/ml) – **PREFERRED BRAND for new patients at NUH and in primary care**
- Inhixa® pre-filled syringes (100mg/mL or 150mg/mL) – **PREFERRED BRAND for new patients at SFH and NHFT**
- Clexane® pre-filled syringes (100mg/mL) – For existing patients only
- Clexane Forte® pre-filled syringes (150mg/mL) – For existing patients only

Arovi® and Inhixa® are the current brands of choice in Nottinghamshire.
****Switching brands should only be undertaken as part of a clinical management plan and should be done with appropriate patient counselling as there are device differences. ****

Different size syringes are available (see table below) and syringes greater than or equal to 60mg contain graduation markings so that part of a whole syringe may be given. Doses are normally given as a single injection from one syringe to prevent multiple injections. The syringe with the closest total quantity to the dose prescribed should be used to minimise the risk of inadvertent overdose (e.g., for a dose of 115mg SC once a day, 120mg syringes should be prescribed). **See appendices 1 (Arovi®) and 2 (Inhixa®).**

Note that Inhixa® and Arovi® colours are different. **Always check the strength carefully before administration and do not rely on colour for identification.**

Arovi® syringe label colour	**Syringe size (100mg/mL)**	**Strength (IU)**	**Inhixa®** syringe label colour
Maroon	20mg	2,000 IU	Light Blue
Yellow	40mg	4,000 IU	Yellow
Orange	60mg	6,000 IU	Orange
Brown	80mg	8,000 IU	Red
Grey	100mg	10,000 IU	Black
	Syringe size (150mg/mL) *		
Purple	120mg	12,000 IU	Purple
Light Blue	150mg	15,000 IU	Dark blue

*The measurable doses are different on the high strength syringes (150mg/mL in the 120mg and 150mg) for Arovi® compared to Inhixa®.

Historical Clexane® prescribing may be continued where clinically appropriate. Clexane® is not one of the preferred brands of choice in Nottinghamshire.

Syringe size (100mg/mL)	**Strength (IU)**	**Clexane®** syringe label colour
20mg	2,000 IU	Light brown
40mg	4,000 IU	Yellow
60mg	6,000 IU	Orange
80mg	8,000 IU	Brown
100mg	10,000 IU	Slate Grey
Syringe size (150mg/mL)		
120mg	12,000 IU	Purple
150mg	15,000 IU	Blue

Clexane® multi-dose vials 300mg/ 3mL are available but not recommended.

Appendix 1: Arovi® - enoxaparin sodium solution for injection measurable doses (in whole mg) – from NUH guidelines

Doses >150mg require a combination of two injections utilising the below measurable single doses.

Enoxaparin sodium (Arovi®) 100mg/mL		
Each 0.025 mL graduation = 2.5 mg enoxaparin		
mg	**Volume (in mL)**	**Syringe - plunger**
20	0.2	20mg - maroon
22	0.225	60mg - orange
25	0.25	60mg - orange
27	0.275	60mg - orange
30	0.3	60mg - orange
32	0.325	60mg - orange
35	0.35	60mg - orange
37	0.375	60mg - orange
40	0.4	40mg - yellow
42	0.425	60mg - orange
45	0.45	60mg - orange
47	0.475	60mg - orange
50	0.5	60mg - orange
52	0.525	60mg - orange
55	0.55	60mg - orange
57	0.575	60mg - orange
60	0.6	60mg - orange
62	0.625	80mg - brown
65	0.65	80mg - brown
67	0.675	80mg - brown
70	0.7	80mg - brown
72	0.725	80mg - brown
75	0.75	80mg - brown
77	0.775	80mg - brown
80	0.8	80mg - brown
82	0.825	100mg - grey
85	0.85	100mg - grey
87	0.875	100mg - grey
90	0.9	100mg - grey
92	0.925	100mg - grey
95	0.95	100mg - grey
97	0.975	100mg - grey
100	1	100mg - grey

Enoxaparin sodium (Arovi®) 150mg/mL		
Each 0.02mL graduation = 3mg enoxaparin		
mg	**Volume (in mL)**	**Syringe - plunger**
102	0.68	120mg - purple
105	0.7	120mg - purple
108	0.72	120mg - purple
111	0.74	120mg - purple
114	0.76	120mg - purple
117	0.78	120mg - purple
120	0.8	120mg - purple
123	0.82	150mg – light blue
126	0.84	150mg – light blue
129	0.86	150mg – light blue
132	0.88	150mg – light blue
135	0.9	150mg – light blue
138	0.92	150mg – light blue
141	0.94	150mg – light blue
144	0.96	150mg – light blue
147	0.98	150mg – light blue
150	1	150mg – light blue

Doses > 150mg will require a combination of two injections utilising measurable single doses shown in the table.

Wherever possible, it is recommended to utilise the least number of mg of enoxaparin to administer the combined dose, to prevent inadvertent overdose.

E.g., a dose of 170mg should be given as 1 x 150mg and 1 x 20mg, rather than 1 x 100mg and 0.7mL from an 80mg syringe.

Appendix 2: Inhixa® - enoxaparin sodium solution for injection measurable dose (matching syringe graduations) – from SFH guidelines

Doses >150mg require a combination of two injections utilising the below measurable single doses.

Enoxaparin sodium (Inhixa®) 100mg/mL		
Each 0.025 mL graduation = 2.5mg enoxaparin		
mg	**Volume (in mL)**	**Syringe - plunger**
10	0.1	60mg - orange
12.5	0.125	60mg - orange
15	0.15	60mg - orange
17.5	0.175	60mg - orange
20	0.2	20mg – light blue
22.5	0.225	60mg - orange
25	0.25	60mg - orange
27.5	0.275	60mg - orange
30	0.3	60mg - orange
32.5	0.325	60mg - orange
35	0.35	60mg - orange
37.5	0.375	60mg - orange
40	0.4	40mg - yellow
42.5	0.425	60mg - orange
45	0.45	60mg - orange
47.5	0.475	60mg - orange
50	0.5	60mg - orange
52.5	0.525	60mg - orange
55	0.55	60mg - orange
57.5	0.575	60mg - orange
60	0.6	60mg - orange
62.5	0.625	80mg - red
65	0.65	80mg - red
67.5	0.675	80mg - red
70	0.7	80mg - red
72.5	0.725	80mg - red
75	0.75	80mg - red
77.5	0.775	80mg - red
80	0.8	80mg - red
82.5	0.825	100mg - black
85	0.85	100mg - black
87.5	0.875	100mg - black
90	0.9	100mg - black
92.5	0.925	100mg - black
95	0.95	100mg - black
97.5	0.975	100mg - black
100	1	100mg - black

Enoxaparin sodium (Inhixa®) 150mg/mL		
Each 0.025mL graduation = 3.75mg enoxaparin		
mg	**Volume (in mL)**	**Syringe - plunger**
101.25	0.675	120mg - purple
105	0.7	120mg - purple
108.75	0.725	120mg - purple
112.5	0.75	120mg - purple
116.25	0.775	120mg - purple
120	0.8	120mg - purple
123.75	0.825	150mg – dark blue
127.5	0.85	150mg – dark blue
131.25	0.875	150mg – dark blue
135	0.9	150mg – dark blue
138.75	0.925	150mg – dark blue
142.5	0.95	150mg – dark blue
146.25	0.975	150mg – dark blue
150	1	150mg – dark blue

Doses > 150mg will require a combination of two injections utilising measurable single doses shown in the table.

Wherever possible, it is recommended to utilise the least number of mg of enoxaparin to administer the combined dose, to prevent inadvertent overdose.

E.g., a dose of 170mg should be given as 1 x 150mg and 1 x 20mg, rather than 1 x 100mg and 0.7mL from an 80mg syringe.

References:

- Inhixa 4,000 IU (40 mg) in 0.4 mL solution for injection in pre-filled syringe SPC. Last updated 10/03/2022. Available at: https://www.medicines.org.uk/emc/product/784/smpc.
- Arovi 4,000 IU (40mg) in 0.4ml solution for injection in pre-filled syringe SPC. Last updated 23/06/2023. Available at: https://www.medicines.org.uk/emc/product/9327/smpc
- RCOG The Acute Management of Thrombosis and Embolism During Pregnancy and the Puerperium (Green-top 37b). April 2015.
- SFHT guideline. Venous thromboembolism (VTE) management guideline for in-patients aged 16 years and older. May 2021.
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- SFHT enoxaparin doses compilation table.
- NUH guideline for the use of enoxaparin in adults for the prevention of thromboembolic events; treatment in adults of deep vein thrombosis/pulmonary embolus (DVT/PE) and sub therapeutic INRs in patients with mechanical heart valves, Review date February 2025.
- NUH guideline for the Management of Acute Thromboembolism in Pregnancy and the Puerperium, review date 2023.
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- NHS England (2023). What is a biosimilar medicine? Available at https://www.england.nhs.uk/long-read/what-is-a-biosimilar-medicine/