Enoxaparin

Section: 10. Medicines affecting the blood > 10.2. Medicines affecting coagulation

ATC codes: B01AB05

Indication	Acute ischaemic heart disease ICD11 code: BA4Z
INN	Enoxaparin sodium
Medicine type	Chemical agent
List type	Core
Formulations	**Parenteral > General injections > SC:** 20 mg per 0.2 mL in prefilled syringe ; 40 mg per 0.4 mL in prefilled syringe ; 60 mg per 0.6 mL in prefilled syringe ; 80 mg per 0.8 mL in prefilled syringe ; 100 mg per 1 mL in prefilled syringe ; 120 mg per 0.8 mL in prefilled syringe ; 150 mg per 1 mL in prefilled syringe ; 150 mg per 1 mL in ampoule ; 20 mg per 0.2 mL in ampoule ; 40 mg per 0.4 mL in ampoule ; 60 mg per 0.6 mL in ampoule ; 80 mg per 0.8 mL in ampoule ; 100 mg per 1 mL in ampoule ; 120 mg per 0.8 mL in ampoule
EML status history	First added in 2015 (TRS 994)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	nadroparin (ATC codes: B01AB06) dalteparin (ATC codes: B01AB04)
Patent information	Patents have expired in most jurisdictions Read more about patents.
Tags	Biological
Wikipedia	Enoxaparin
DrugBank	Enoxaparin

Summary of evidence and Expert Committee recommendations

An application was submitted for the inclusion of low-molecular weight heparins (LMWHs) on the Model List of Essential Medicines for three indications: ■ prophylaxis of venous thromboembolism (VTE) in hospitalized patients; ■ treatment of VTE; and ■ treatment of acute coronary syndromes. The Committee noted that heparin sodium (unfractionated heparin (UFH)) has been on the EML since 1977 and that LMWHs had not previously been evaluated for inclusion on the EML. Venous thromboembolism is a frequent disease and a major health problem: the annual incidence rate was estimated to vary from 57 to 133 per 100 000 persons in different continents (1-3). It is associated with long-term clinical sequelae, including chronic thromboembolic pulmonary hypertension and post-thrombotic syndrome – a cluster of symptoms (pain, cramps, heaviness, paraesthesia, pruritus) and signs (pretibial oedema, skin induration and hyperpigmentation, venous ectasia) that can have a significant impact on quality of life. Case-fatality rates after a first VTE event have been estimated to be 5% (95% CI: 1–9%) after an idiopathic event, 7% (95% CI: 2–13%) after a VTE provoked by trauma, surgery or immobilization, and 25% (95% CI: 15–36%) in patients with cancer (4). The incidence of first-time VTE rises exponentially with age (5). Ethnicity is another major determinant, with higher incidence of VTE and pulmonary embolism in white persons and African-Americans than in Asians and Pacific Islanders (6,7). A large cross-sectional survey of hospital inpatients in 32 countries found 51.8% of patients to be at risk for VTE (8). Surgical procedures, in particular major orthopaedic

surgery and cancer surgery, are commonly complicated by VTE (9). Low-dose UFH has been the standard treatment of VTE for several years. It has a rapid onset of action but requires frequent laboratory monitoring, dose titration and multiple injections per day. In contrast, LMWHs can be administered once or twice daily in fixed, weight-adjusted doses, limiting the need for laboratory monitoring to attain the recommended dose in selected patients (e.g. renal failure, young children, obese patients, pregnant women). Prophylaxis of venous thromboembolism in surgical patients: Several randomized controlled trials have tested LMWHs against various comparators in different surgical populations. Evidence is usually stratified according to orthopaedic and non-orthopaedic surgery since the risk of VTE differs between the two populations, with orthopaedic patients being at greater risk. As the evidence has accumulated across both settings and the confidence in benefit has increased, LMWHs have become the standard prophylaxis (10). In general and specialized surgery (e.g. gastrointestinal, gynaecological, laparoscopic, thoracic, urological, orthopaedic (including total hip or knee arthroplasty and hip fracture surgery), LMWHs are clearly more effective than no prophylaxis for reducing the risk of symptomatic VTE and pulmonary embolism (relative risk reduction approximately 80%). They are at least as effective as UFH for prevention and treatment of VTE (11-13). When used for perioperative thromboprophylaxis in cancer patients undergoing surgery, LMWHs and UFH show only limited differences for preventing mortality, pulmonary embolism, deep vein thrombosis or bleeding outcomes (14). For initial anticoagulation, LMWHs are often preferred to other interventions such as mechanical prophylaxis, vitamin K antagonists and aspirin (12, 15). With regard to safety, LMWHs have been associated with haemorrhagic and non-haemorrhagic complications. Meta-analyses of trials comparing LMWHs with no prophylaxis in hip fracture surgery, hip and knee replacement surgery, and general surgery have shown that LMWHs approximately double the risk of major bleeding and wound haematoma (from a baseline level of 1%) (11, 13). The expected risk of major bleeding with LMWHs has been shown to be very close to that with UFH. In a network meta-analysis, LMWH and UFH were indirectly compared using no prophylaxis and other interventions as the reference comparator: LMWH did not significantly increase bleeding, while UFH did (12, 13). Several factors influence the incidence of heparin-induced thrombocytopenia (HIT), a potentially severe complication, including the type and preparation of heparin (UFH or LMWH) and the heparin-exposed patient population, with postoperative patients presenting a higher risk. A Cochrane systematic review compared the incidence of HIT after exposure to UFH or LMWH following any surgical intervention: LMWHs were associated with a reduction in the risk of HIT compared with UFH (16). The costs of prophylactic doses of LMWHs ranged from US$ 2.25 to US$ 18.5 per dose, depending on dose and type of heparin. Biosimilar LMWHs can be found at lower prices. Studies assessing the cost–effectiveness of VTE prophylaxis in hospitalized patients have been carried out in Australia, Europe and North America. The use of pharmacological prophylaxis in hospital settings has been associated with substantial cost savings (17-21). Treatment of venous thromboembolism: A Cochrane systematic review compared LMWH with UFH for the initial treatment of VTE (22). Fixed-dose LMWH was found to be more effective than adjusted-dose UFH in reducing the risk of recurrent VTE during both initial treatment and follow-up. Moreover, overall mortality was significantly reduced. Compared with UFH, LMWH is associated with 15 fewer recurrent VTE events and 10 fewer deaths from any cause per 1000 patients (23). Major bleeding during the initial phase of treatment was significantly reduced with LMWH compared with UFH, with an incidence of 1.1% versus 1.9% (22). The advantage of LMWH can be summarized as five fewer major bleeding episodes per 1000 patients (23). In patients with active cancer and pregnant women, LMWHs are preferred to other agents (UFH, warfarin) because they have a more favourable safety profile. The American College of Chest Physicians (ACCP) recommends initial treatment of acute VTE with parenteral anticoagulation (LMWH, fondaparinux, UFH) and recommends LMWHs over intravenous or subcutaneous UFH (23). The greater efficacy and favourable safety profile of LMWHs, together with their greater ease of use, mean patients with acute VTE of the leg, whose home circumstances are adequate, can be treated at home with LMWHs rather than in hospitals (24). For these reasons, LMWHs are likely to be preferred by patients. Treatment of acute coronary syndromes: Acute coronary syndrome (ACS) refers to a spectrum of clinical presentations related to acute myocardial ischaemia caused by atherosclerotic coronary disease; it includes ST-elevation myocardial infarction (STEMI), non ST-elevation myocardial infarction (NSTEMI), and unstable angina (UA). It is the most common cause of death worldwide: ischaemic heart disease accounted for 7.4 million deaths worldwide in 2012 (25). The proportion of deaths is higher in high-income countries but it is rapidly increasing in lower-middle income countries. The percentage of ACS or MI cases with ST-segment elevation varies in different registries and depends on the age of patients

considered and the surveillance systems, varying from 30% to 50% (26). In recent years there has been a progressive increase in the proportions of patients who present with UA compared with acute MI and with NSTEMI compared with STEMI. In industrialized countries the annual incidence of UA is around six cases per 10 000 people (27). UFH has been in use as therapy for patients with NSTEMI or UA for more than two decades, and as an adjunctive therapy to fibrinolysis or percutaneous coronary intervention in STEMI. Non-ST elevation ACS Based on evidence for UFH and LWMHs, anticoagulant therapy is superior to no anticoagulant therapy in patients with non-ST elevation ACS (28, 29). Enoxaparin had a significantly lower rate of the combined end-point of death, MI, and angina compared with UFH in patients with UA or NSTEMI who were treated with a conservative medical approach (30-32). Other LMWHs appear to have equivalent efficacy to UFH, but possible differences with enoxaparin cannot be excluded. In patients who underwent percutaneous coronary revascularization or coronary artery bypass graft surgery, evidence favouring enoxaparin is less straightforward: enoxaparin and UFH have similar efficacy (33) but enoxaparin might be associated with a significant increase in major bleeding (34). Nevertheless, enoxaparin is easier to administer than UFH and does not require laboratory monitoring. ST-elevation ACS: A systematic review compared the efficacy and safety of LMWH with UFH across the spectrum of ACS (35). LMWH was found to be associated with a statistically significant lower risk of death or MI at 30 days. Across the entire ACS spectrum, LWMH (enoxaparin) reduced the risk of death or MI from 13.5% to 12.5%, with a better efficacy profile in patients with STEMI. Another systematic review compared LMWH (enoxaparin) with UFH in the context of primary percutaneous coronary intervention in STEMI; LMWH was associated with significant reductions in death (1.66% absolute risk reduction) and MI (33). In patients with STEMI, NSTEMI or UA, differences in major bleeding were slightly more frequent in patients treated with UFH compared with those treated with LWMH (33). Notably, during percutaneous coronary interventions, the evidence is inconsistent: major bleeding might be more frequent with UFH or LWMHs depending on route of administration (i.e. intravenous or subcutaneous enoxaparin) and other variables (33, 34). In patients with ACS, LMWH (enoxaparin) is a cost–effective strategy, both improving important clinical outcomes and saving money relative to therapy with standard UFH (36). However, drug acquisition costs per day for LMWH can be higher than the costs for UFH. The adoption of LMWH necessitates demonstration of economic attractiveness over UFH, taking into account other associated costs occurring throughout the continuum of care (e.g. advantages related to there being no need for laboratory monitoring and to safety of administration in outpatient settings). The European Society of Cardiology guidelines on the management of NSTEMI or UA recommend the use of anticoagulant therapy for all patients in addition to antiplatelet therapy (37). In the management of STEMI, guidelines recommend anticoagulation in patients treated with thrombolytics until revascularization (if performed) or for the duration of hospital stay up to 8 days. LMWH is preferred to UFH (38). In patients with severe renal insufficiency, repeated doses of LMWH may lead to accumulation and increased risk of bleeding, as LMWH is primarily renally cleared. Dose adjustment may be required. Older and obese patients may also require dose-adjustments of LMWH. LMWH is safe for use during pregnancy and pregnant patients can be given the same dose as non-pregnant patients. In the event of significant increase in maternal weight, however, dose adjustments may be required (39). LMWH offers several pharmacological advantages over UFH, including better absorption after subcutaneous administration, less protein binding and a more predictable dose–effect relationship. LMWHs are similar products but are not identical and they can differ chemically and pharmacokinetically (40). A wide spectrum of in vitro and in vivo coagulation tests detected some measurable pharmacodynamic differences between currently available LMWH preparations when administered using equivalent anti-activated factor Xa doses. Evidence from a small number of studies that directly compared different LMWHs in VTE has shown no clinically meaningful differences. Overall, the Expert Committee considered that the available evidence showed that LMWHs are safe and effective in the prophylaxis and treatment of VTE, and in the treatment of acute coronary syndromes. Being administered subcutaneously, they are also easier to use than IV unfractionated heparin. No routine monitoring is required, which adds to their convenience. The Committee agreed that LMWHs meet the criteria for inclusion as an essential medicine in health systems and therefore recommended addition of the pharmacological class of LMWHs to the core list of the Model List of Essential Medicines. The Committee considered that, as there is more evidence for its effectiveness and safety, enoxaparin should be listed with a square box symbol as representative of the class. The Committee recommended a note limiting alternatives to nadroparin and dalteparin, since the available evidence supports

their use in the three indications for which listing was sought. The Committee considered cost and noted the availability of cheaper, biosimilar generic alternatives. References: 1. Martinez C, Cohen AT, Bamber L, Rietbrock S. Epidemiology of first and recurrent venous thromboembolism: a population-based cohort study in patients without active cancer. Thromb Haemost. 2014;112(2):255-63. 2. Spencer FA, Emery C, Lessard D, Anderson F, Emani S, Aragam J, et al. The Worcester Venous Thromboembolism study: a population-based study of the clinical epidemiology of venous thromboembolism. J Gen Intern Med. 2006;21(7):722-7. 3. Ho WK, Hankey GJ, Eikelboom JW. The incidence of venous thromboembolism: a prospective, community-based study in Perth, Western Australia. Med J Aust. 2008;189(3):144-7. 4. Cushman M, Tsai AW, White RH, Heckbert SR, Rosamond WD, Enright P, et al. Deep vein thrombosis and pulmonary embolism in two cohorts: the longitudinal investigation of thromboembolism etiology. 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