Therapeutic Class Overview
Injectable Anticoagulants

Therapeutic Class

- **Overview/Summary:** The injectable anticoagulants include dalteparin (Fragmin®), enoxaparin (Lovenox®), and fondaparinux (Arixtra®). Dalteparin and enoxaparin are classified as low molecular weight heparins (LMWH), and fondaparinux is a selective factor Xa inhibitor. In general, the injectable anticoagulants are Food and Drug Administration (FDA)-approved for prophylaxis and/or treatment of venous thromboembolism (VTE). Certain agents in the class are also FDA-approved for the treatment of acute ST-segment elevation myocardial infarction (STEMI) or for prophylaxis of ischemic complications in unstable angina and non-Q-wave myocardial infarction. The specific FDA-approved indications for the injectable anticoagulants are outlined in Table 1.[1-3]

  The LMWH agents exert their anticoagulant effect by binding to antithrombin, an endogenous inhibitor of various activated clotting factors, including factor Xa and thrombin. A LMWH is a smaller fragment of unfractionated heparin (UFH) that is formed by enzymatic or chemical depolymerization processes. The difference in the average size of LMWH (5,000 daltons) compared to UFH (3,000 to 30,000 daltons) contributes to the pharmacologic differences between the agents. The LMWH agents primarily inhibit factor Xa, and do so with much less effect on thrombin compared to UFH. The inhibition of thrombin requires a heparin molecule to bind simultaneously to antithrombin and thrombin to form a ternary complex. The UFH molecules are large enough for this to occur while the LMWH molecules typically are not.[4,5] Fondaparinux is a synthetic factor Xa inhibitor that was developed to have an increased affinity to antithrombin. Its specific anti-factor Xa activity is higher than that of the LMWH agents. Because the LMWH agents are prepared using different methods of depolymerization, they differ somewhat in their pharmacokinetic properties and anticoagulant profiles. Therefore, these agents are not clinically interchangeable[5]

Table 1. Current Medications Available in the Therapeutic Class[1-3]

Generic Name (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Dalteparin (Fragmin®)	Extended treatment of symptomatic venous thromboembolism (proximal deep vein thrombosis and/or pulmonary embolism) in patients with cancer*, prophylaxis of ischemic complications in unstable angina and non-Q-wave myocardial infarction†, prophylaxis of deep vein thrombosis which may lead to pulmonary embolism in medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness, in patients undergoing abdominal surgery who are at risk for thromboembolic complications and in patients undergoing hip fracture surgery	Syringe: 2,500 IU/0.2 mL‡ 5,000 IU/0.2 mL‡ 7,500 IU/0.3 mL‡ 10,000 IU/1 mL§ 12,500 IU/0.5 mL‡ 15,000 IU/0.6 mL‡ 18,000 IU/0.72 mL‡ 95,000 IU/3.8 mL‖	-
Enoxaparin (Lovenox®¶)	Prophylaxis of ischemic complications in unstable angina and non-Q-wave myocardial infarction†, prophylaxis of deep vein thrombosis which may lead to pulmonary embolism in medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness, in patients undergoing abdominal surgery who are at risk for thromboembolic complications, in	Syringe (100 mg/mL): 30 mg/0.3 mL‡ 40 mg/0.4 mL‡ 60 mg/0.6 mL§ 80 mg/0.8 mL§ 100 mg/1 mL§ 300 mg/3 mL‡‡	✔

Generic Name (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
	patients undergoing hip replacement surgery[#], in patients undergoing knee replacement surgery, treatment of acute deep vein thrombosis**, treatment of acute ST-segment elevation myocardial infarction[††]	Syringe (150 mg/mL): 120 mg/0.8 mL[§] 150 mg/1 mL[§]	
Fondaparinux (Arixtra®[¶])	Prophylaxis of deep vein thrombosis which may lead to pulmonary embolism in patients undergoing abdominal surgery who are at risk for thromboembolic complications, in patients undergoing hip fracture surgery[§§], in patients undergoing hip replacement surgery, in patients undergoing knee replacement surgery, treatment of acute deep vein thrombosis[‖‖], treatment of acute pulmonary embolism[¶¶]	Syringe: 2.5 mg/0.5 mL[‡] 5 mg/0.4 mL[‡] 7.5 mg/0.6 mL[‡] 10 mg/0.8 mL[‡]	✔

IU=international units
*In these patients therapy begins with the initial venous thromboembolism treatment and continues for six months.
†When concurrently administered with aspirin therapy.
‡Available as a single-dose prefilled syringe.
§Available as a single-dose graduated prefilled syringe.
‖Available as a multiple-dose vial. After first penetration of the rubber stopper, store the multiple-dose vials at room temperature for up to two weeks.
¶Generic available in at least one dosage form and/or strength.
#During and following hospitalization.
**Indicated for inpatient treatment of acute deep vein thrombosis with or without pulmonary embolism, when administered in conjunction with warfarin, and for outpatient treatment of acute deep vein thrombosis without pulmonary embolism when administered in conjunction with warfarin.
††When administered concurrently with aspirin, enoxaparin has been shown to reduce the rate of the combined endpoint of recurrent myocardial infarction or death in patients with acute ST-segment elevation myocardial infarction receiving thrombolysis and being managed medically or with percutaneous coronary intervention.
‡‡Available as a multi-dose vial.
§§Including extended prophylaxis.
‖‖When administered in conjunction with warfarin.
¶¶When administered in conjunction with warfarin when initial therapy is administered in the hospital.
***With or without pulmonary embolism when administered in conjunction with warfarin.

Evidence-based Medicine

- Currently, dalteparin is the only injectable anticoagulant approved for the extended treatment of VTE in patients with cancer. In a trial comparing dalteparin to oral anticoagulation (warfarin or acenocoumarol [not available in the United States]) in patients with symptomatic VTE, the incidence of symptomatic, recurrent VTE was significantly lower with dalteparin at six months. At six months there was no difference in mortality rates between the two treatments; however, a 12 month follow-up revealed a significant benefit in mortality with dalteparin in patients without known metastases of their cancer.[22,23]
- A Cochrane Review that included 16 randomized-controlled trials of cancer patients receiving initial treatment suggest that LMWH agents may be “superior” to UFH for the initial treatment of VTE in cancer patients due to an observed nonsignificant advantage of these agents for reducing the incidence of recurrent VTE.[23]
- The evidence establishing the safety and efficacy of the injectable anticoagulants for VTE treatment and/or thromboprophylaxis is well established.[27-78]
- Several placebo-controlled trials, meta-analyses, and systematic reviews with the various injectable anticoagulants in medical patients, immobilized patients, and those undergoing an orthopedic surgery have been conducted and consistently demonstrate their efficacy.[28-31,36-42,57,67,75,77-78]
- When the injectable anticoagulants are compared to other methods of treatment and thromboprophylaxis which include heparin, UFH, and warfarin, “superiority” in terms of recurrent VTE

and safety is not always consistent, which supports recommendations from current clinical guidelines.[32,33,47-55,68-74]

- Treatment with fondaparinux appears to be associated with a lower incidence of VTE, and a comparable incidence of major bleeding compared to enoxaparin.[59-62]
- In a meta-analysis of randomized-controlled trials comparing fondaparinux to LMWH therapy (enoxaparin), the incidence of VTE was significantly less and the incidence of major bleeding was significantly greater with fondaparinux.[63]

Key Points within the Medication Class

- According to Current Clinical Guidelines: [8-16]
    - LMWH, fondaparinux, apixaban (Eliquis®), dabigatran (Pradaxa®), rivaroxaban (Xarelto®), low dose UFH, adjust-dose vitamin K antagonist (VKA) therapy, aspirin, or an intermittent pneumatic compression device is recommended in patients undergoing total hip or knee arthroplasty.
    - Use of LMWH, fondaparinux, low dose UFH, adjusted-dose VKA therapy, aspirin, or an intermittent pneumatic compression device is recommended in patients receiving hip fracture surgery. In these orthopedic surgeries thromboprophylaxis is recommended for a minimum of 10 to 14 days; however, for major orthopedic surgeries it is suggested to extend thromboprophylaxis in the outpatient period for up to 35 days from the day of the surgery.
    - For total hip or knee arthroplasty and hip fracture surgery, thromboprophylaxis with LMWH is suggested in preference to the other recommended agents.
    - For patients who decline or who are uncooperative with injections or intermittent pneumatic compression devices, apixaban or dabigatran is recommended over alternative forms of thromboprophylaxis, with rivaroxaban or adjusted-dose VKA therapy recommended if these two therapies are unavailable.
    - Non-orthopedic surgical patients (e.g., general and abdominal-pelvic surgery) at moderate to high risk for VTE, who are not at high risk for bleeding complications, should receive thromboprophylaxis with LMWH or low dose UFH, and extended (four weeks) LMWH is recommended in high risk non-orthopedic surgical patients with cancer who are not otherwise at high risk for major bleeding complications.
    - For prevention of VTE in nonsurgical patients (i.e., medical patients), thromboprophylaxis with LMWH, low dose UFH, or fondaparinux is recommended in acutely ill hospitalized patients at increased risk of thrombosis.
    - Clinical guidelines also recommend the use of LMWH, fondaparinux, UFH, or bivalirudin (a direct thrombin inhibitor) for the management of a non-ST-segment elevated acute coronary syndrome. The use of a specific agent over another is based on individual patient risk factors, as well as the timing and intensity of other planned management strategies. In addition, it appears that fondaparinux has a more favorable safety and efficacy profile compared to LMWH in certain clinical situations, including patients at high-risk for bleeding.

- Other Key Facts:
    - Currently, enoxaparin and fondaparinux are the only injectable anticoagulants that are available generically.

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