

Indiana Medicaid Therapeutics Committee Therapeutic Class Review Summary

Therapeutic Class:

Heparin and Related Preparations

Overview:

Heparin is a widely used parenteral anticoagulant derived from porcine or bovine tissue. It was discovered in 1916 and FDA approved in 1939. Heparin acts as a catalyst to markedly accelerate the rate at which antithrombin III (heparin cofactor) neutralizes thrombin (factor IIa) and activated coagulation factor X (Xa). Full therapeutic doses of heparin prolong clotting time but not bleeding time; only at high doses does heparin interfere with platelet aggregation.

Heparin, administered intravenously (IV) or subcutaneously (SC), is indicated in the prophylaxis and treatment of venous thromboembolism (VTE), the prophylaxis and treatment of pulmonary embolism (PE), the prophylaxis and treatment of peripheral arterial embolism, atrial fibrillation with embolization, the diagnosis and treatment of acute and chronic consumption coagulopathies, prophylaxis of deep vein thrombosis (DVT) and PE in patients undergoing abdominal or thoracic surgery, the prophylaxis of DVT in patients who are at risk for thromboembolic complications, and the prevention of clotting in arterial and heart surgery, blood transfusions, extracorporeal circulation, dialysis procedures and blood samples. Heparin is often considered the drug of choice for anticoagulation in pregnancy; because of its large molecule size, it does not cross the placenta and is not secreted in breast milk. The major adverse event seen with heparin therapy is hemorrhage. Other adverse events of concern are heparin-induced thrombocytopenia, osteoporosis, and other bleeding events.

In 1976, it was reported that low-molecular-weight heparin (LMWH) fractions prepared from standard heparin displayed a lesser effect on the activated partial thromboplastin time (aPTT) while still inhibiting factor Xa. LMWHs exert their anticoagulant effect via the inhibition of Xa, and to a lesser degree thrombin. LMWHs were first evaluated for the prevention of DVT in high-risk surgical patients in the mid-1980s. Meta-analysis has shown that LMWHs given once daily are at least as effective and safe as low-dose unfractionated heparin (UFH) given 2-3 times daily for the prevention of DVT following orthopedic surgery. At recommended doses, LMWHs do not significantly affect platelet activity or bleeding time. The safety and efficacy of the LMWHs in pregnancy have not been adequately evaluated. The LMWHs currently available in the United States are enoxaparin (March 1993), dalteparin (December 1994), and tinzaparin (July 2000).

There are some advantages of LMWHs over UFH: 1) more predictable pharmacokinetics, and thus a more predictable anticoagulant response; 2) longer half-life after SC administration, allowing once daily dosing; 3) a lower incidence of heparin induced thrombocytopenia; 4) a lower incidence of osteopenia (although osteoporosis may still occur); 5) ability to manage VTE in an outpatient environment. In human clinical studies the bleeding rates with LMWHs have been similar to those seen with UFH.

Dalteparin was recently approved for extended treatment of symptomatic VTE to reduce the recurrence of VTE in patients with cancer. Additionally, Dalteparin is approved for the prevention of DVT in patients undergoing hip replacement surgery or abdominal surgery, prevention of DVT in medical patients who are at risk for thromboembolic complications, and prophylaxis of ischemic complications in unstable angina and non-Q-wave myocardial infarction, when concurrently administered with aspirin therapy. Tinzaparin is approved only for the treatment of acute, symptomatic DVT with or without PE in conjunction with warfarin. Enoxaparin is approved for the indications given for tinzaparin and dalteparin, but is not approved for extended treatment of symptomatic VTE. Enoxaparin is also indicated for

prophylaxis of DVT in patients undergoing knee replacement surgery, and was recently approved for treatment of acute ST-segment elevation myocardial infarction (STEMI).

Fondaparinux is the first agent in a new class of anticoagulants. It selectively inhibits factor Xa, but does not inactivate thrombin (factor IIa). Fondaparinux was FDA-approved in December of 2001 and has the following indications: prevention of DVT in hip replacement, knee replacement, hip fracture, and abdominal surgeries; treatment of acute DVT in conjunction with warfarin; and treatment of acute PE in conjunction with warfarin. In clinical trials, fondaparinux has shown greater efficacy in prevention of VTE over enoxaparin; however, in knee replacement surgery, major bleeding was statistically greater with fondaparinux.

Historically, the use of parenteral anticoagulants was seen mainly in the hospital. However, the advent of LMWHs allowed once daily SC administration that can be self-administered in the outpatient environment. The results of clinical studies appear to support the use of various LMWHs in the outpatient environment for extended postoperative prophylaxis of VTE, perioperative anticoagulation, and outpatient management of PE or DVT. Furthermore, the Sixth American College of Chest Physicians (ACCP) Consensus Conference on Antithrombotic Therapy includes the following recommendations:

- Outpatient prophylaxis with LMWH should be offered beyond 7-10 days after major orthopedic surgery, at least for high-risk patients (grade 2A recommendation*).
- In the treatment of VTE disease, LMWH regimens are preferred over UFH.
- LMWH regimens for the treatment of VTE can be used as outpatient therapy with minimal requirements: stable proximal DVT or PE; normal vital signs; low risk of bleeding; absence of severe renal insufficiency; availability of a practical system for administering LMWH and warfarin, with appropriate monitoring; availability of a practical system for surveillance and treatment of recurrent VTE and bleeding complications.

Generic Name	Brand Name	Manufacturer	Generic Available
Dalteparin	Fragmin [®]	Pharmacia	No
Enoxaparin	Lovenox [®]	Aventis	No
Fondaparinux	Arixtra [®]	GlaxoSmithKline	No
Heparin	Generics	Various	Yes
Tinzaparin	Innohep [®]	Pharmion	No

Summary:

Heparin is available generically and will remain widely used in a number of conditions requiring anticoagulation. Clinical trials comparing LMWHs have shown equivalent efficacy and safety. Enoxaparin, which recently gained approval for the treatment of acute ST-segment elevation myocardial infarction (STEMI), has the greatest number of FDA approved indications and the most clinical experience. Dalteparin was recently approved for extended treatment of symptomatic VTE to reduce the recurrence of VTE in patients with cancer. Additionally, dalteparin has the advantage of offering once daily dosing for all indications. Fondaparinux has shown potential superior efficacy in DVT prevention after hip replacement, knee replacement and hip fracture; however, it may have a greater incidence of bleeding. Selection of an agent for the preferred drug list should be based upon FDA-approved indications, potential use in the outpatient environment, adverse reaction profile and the total cost impact to the program.

*Recommendation is based on a framework that captures the tradeoff between benefits and risks. Grade 2A states that the clarity of the risks and benefits are unclear. Only randomized controlled trials without important limitations have been conducted.