Generic Enoxaparin Questions and Answers

1. What is FDA doing today about the drug enoxaparin?

Today, FDA is approving an abbreviated new drug application (ANDA) for enoxaparin sodium for injection. The product is a generic version of Lovenox. The application was submitted by Sandoz, Inc, in partnership with Momenta Pharmaceuticals. We are also responding to a citizen petition submitted on behalf of Aventis Pharmaceuticals, Inc. requesting that we withhold approval of any ANDA for generic enoxaparin sodium for injection unless certain conditions are met.

2. What is enoxaparin?

Enoxaparin is available as an injectable medicine that helps prevent blood clots in the legs and other parts of the body. If these blood clots are not prevented, they can travel to the lungs and cause serious complications and even death. After a patient has surgery, such as hip or knee replacement or in some cases abdominal surgery, enoxaparin is often used for several days to up to a month to prevent blood clots. This medicine is also used to prevent blood clots in patients confined to bed and also for patients experiencing chest pain and heart attacks. Enoxaparin belongs to a class of drugs known as “low molecular weight heparin” (LMWH), which is different than heparin, another drug that helps to prevent blood clots.

3. What is the difference between LMWH and heparin?

LMWH and heparin are both used to prevent blood from clotting inside the body, but are used in different situations.

- Heparin, sometimes called “standard heparin,” is available as a liquid solution injected directly into the blood (intravenous or “IV”) and only given to hospitalized patients, for instance, to prevent blood clots during surgery. Because patients respond widely to heparin sodium, laboratory monitoring of anticoagulant activity is needed to adjust the dose of heparin and monitor its effect in the hospital. In addition, heparin has potential to cause a possibly deadly condition known as Heparin Induced Thrombocytopenia (HIT), where the body stops producing blood platelets. Thus, in the hospital, doctors can notice HIT right away and take action to reverse the condition. Doctors or other healthcare professionals must inject a patient with heparin. Patients cannot use heparin themselves.

- LMWH, such as enoxaparin, is made from heparin. It is also available as a liquid injectable solution used to prevent blood clots, but is used differently than heparin. LMWH produces a more predictable anticoagulant response so frequent monitoring is not needed to adjust the dose. LMWH is also designed to last much longer in the body, so it does not need to be injected intravenously. Instead, LMWH is injected under the skin. Additionally, LMWH has a lower incidence of HIT. Because LMWH has more predictable efficacy and a lower incidence of adverse effects such as HIT, patients can inject LMWH themselves at home (although it is also often used in the hospital).

4. How is enoxaparin marketed?

Enoxaparin is marketed under the brand name Lovenox, and will now also be marketed as a generic drug under the name enoxaparin sodium for injection.

5. Why is a generic version of Lovenox important?

Generic medications approved by FDA are as safe and effective as their brand name counterparts and are usually much less expensive and offer alternatives to patients and prescribers.

6. Is FDA approving the first generic version of any Low Molecular Weight Heparin (LMWH) product?

Yes. There are other brands of LMWH products, but no other generic versions of Lovenox nor any other generic version of brand name LMWH products. The currently available brands of LMWH approved by FDA in the United States are:

- Lovenox generic name, enoxaparin manufactured by Sanofi-Aventis
- Fragmin generic name, dalteparin manufactured by Pfizer
- Innohep generic name, tinzaparin manufactured by Celgene

FDA has determined that none of these brand products can be used interchangeably with one another. This means that when a doctor writes a prescription for one of these brand products, a pharmacist should not substitute another brand product when filling the prescription without checking with the physician. However, FDA has determined that Sandoz’s generic enoxaparin can be substituted for Lovenox.
7. Applications to FDA for approval of generic enoxaparin were submitted in the early to mid 2000s. Why has it taken so long for FDA to approve a generic version of enoxaparin?

Approval of generic enoxaparin has involved a variety of challenges including:

- Determining whether FDA could accept an application for generic enoxaparin, given its complex chemical structure;
- Demonstrating "sameness" to the brand name product and its likelihood of producing immunogenic reactions;
- Addressing the potential for contamination of heparin, from which LMWH, such as enoxaparin, is produced.

Each bullet above is discussed further in the next three questions below.

8. How did the complex chemical structure of enoxaparin affect generic approval?

Enoxaparin is a complex mixture of oligosaccharides (chains of sugar) that vary in chemical structure and size. It is made from heparin by chemically breaking up the larger heparin chains into smaller fragments. The complex chemical features of enoxaparin are determined by both the qualities of the heparin and the chemical process used to cleave the heparin into enoxaparin. Unlike most traditional drugs (often called "small-molecule" drugs) that have relatively simple chemical structures that are easily characterized, it is much more challenging to demonstrate that a generic enoxaparin sodium product contains the same active ingredient as Lovenox. Generic enoxaparin sodium must have the same active ingredient as Lovenox. FDA scientists established a scientific approach for demonstrating active ingredient sameness that takes into consideration the complexity of enoxaparin. This scientific approach is reflected in five criteria, which involve (1) the physical and chemical characteristics of enoxaparin, (2) the nature of the heparin material and the chemical process used to break up heparin chains into smaller pieces, (3) the nature and arrangement of components that constitute enoxaparin, (4) certain laboratory measurements of the product's anticoagulant activity, and (5) certain aspects of the drug's effect in humans. These five criteria ensure that a generic enoxaparin drug product will have the same effects as the brand-name drug product when injected into a patient.

9. Why does FDA expect generic manufacturers of enoxaparin to conduct immunogenicity studies?

Standard heparin is known to cause adverse reactions called immunogenic responses, such as Heparin Induced Thrombocytopenia (HIT). LMWH is made from standard heparin but is associated with a lower rate of HIT than standard heparin. FDA expects sponsors of generic enoxaparin products to demonstrate that their manufactured versions do not have any higher risk of these or other dangerous reactions than Lovenox. Although conducting immunogenicity testing for this product can be an extensive and time-consuming process for a manufacturer, all manufacturers of generic enoxaparin are expected to do this as part of the application process. These studies evaluated impurities using physiochemical and biological assays.

10. Were the heparin contamination issues in 2008 taken into account for FDA approval of enoxaparin?

In early 2008, there was a severe medication crisis in the U.S. associated with contaminated standard heparin and linked to contaminated materials from China. There were 246 reported deaths in the United States following administration of heparin between January 1, 2007, and May 31, 2008, 238 of which were reported to the FDA in 2008. More information on adverse event reports and heparin. Because enoxaparin is made from standard heparin, it is important to ensure that the enoxaparin products have not been contaminated, and that the manufacturing processes for heparin and enoxaparin will meet rigorous production standards to avoid future contamination. FDA has been inspecting all manufacturers' heparin production facilities in China that make heparin related products for the U.S. market, because materials from China were found to be the source of the contaminated heparin in 2008, requiring corrective actions as appropriate. FDA used these inspections to assess whether heparin production facilities have adequate controls to prevent contamination or other quality defects. Inspections conducted by FDA revealed some suppliers of heparin material for the U.S. market were not in compliance with current good manufacturing practices (CGMP) or receiving material from reliable sources. Inspections of production facilities involved in Sandoz's generic enoxaparin product determined that these manufacturing operations satisfy CGMP standards.

11. Have inspections of all Chinese manufacturing plants that make enoxaparin been consistently conducted by FDA officials?

Yes. FDA inspects both domestic and foreign manufacturing facilities to assess compliance with current good manufacturing practice (CGMP). The CGMP requirements for drugs include requirements for the methods, facilities, and controls used in manufacturing, processing, and packing of a drug. CGMP requirements help to assure the identity, strength, quality, and purity of drugs.

The approval process for generic drug marketing applications, including those for generic enoxaparin, includes a review of the manufacturer's compliance with CGMP. FDA investigators determine whether the firm has the necessary facilities methods, and controls to manufacture the drugs. Decisions regarding compliance with CGMP regulations are based upon inspection of the facilities, sample analyses, and compliance history of the company. Manufacturers are held to the same standards by FDA to assure the identity, strength, quality, and purity of drugs.

12. Is generic enoxaparin the first product approved in the U.S. that is a generic drug derived from animal sources?

No. In addition to enoxaparin (which is made from heparin derived from pig intestines), other products made from animal sources have been approved as generic products under the Federal Food, Drug, and Cosmetic Act (FFDCA), the same law that governs chemically-manufactured drugs. For example, FDA has approved generic versions of standard...
heparin for many years.

13. What is the subject of the Citizen Petition to FDA about generic enoxaparin?
In 2003, the manufacturer of brand name Lovenox, Aventis Pharmaceuticals (now known as Sanofi-Aventis) submitted a Citizen Petition to FDA asking FDA to refuse to approve any generic version of enoxaparin unless certain conditions are met (see link below). During the next four years, through June of 2007, Aventis followed up its Citizen Petition with four different supplements containing additional arguments against generic approval of enoxaparin that FDA also considered. Through April of 2009, Aventis also added eight sets of comments regarding the Citizen Petition. FDA has carefully evaluated these scientific and legal arguments, and has concluded that a generic version of enoxaparin can be approved.

FDA’s response to the Citizen Petition (PDF - 348KB).

14. The European Union issued guidelines for generic LMWH that require clinical studies for approval. Why is FDA allowing generic LMWHs without requiring clinical studies?
Although FDA regularly takes note of the actions of other national or international regulatory authorities, those actions do not constrain our decision-making. Different regulatory authorities, such as the European Medicines Agency (EMA), have different standards and procedures for the review and approval of drugs and biological products. The differences in the regulatory standards and procedures between EMA and FDA have resulted in different requirements for approval of generic versions of LMWH products (e.g., enoxaparin), as explained below.

The EMA has set guidelines for LMWH products such as enoxaparin that only require the products to contain a similar (as opposed to the same) active ingredient to that contained in another already marketed LMWH product. Because the proposed LMWH product in Europe will contain an active ingredient that is similar to (as opposed to the same as) the brand name product, there might be uncertainties as to whether the two products are the same with regard to safety and effectiveness. Thus, sponsors of a similar enoxaparin product under the EMA framework are expected to provide clinical studies showing comparable effectiveness to the proposed similar LMWH product as well as clinical data showing comparable safety (including with respect to Heparin Induced Thrombocytopenia).

In contrast, FDA requires a generic enoxaparin product to contain the same active ingredient as Lovenox. Based upon the FDA’s scientific experience and expertise, and relevant scientific information, FDA has concluded that the five criteria (see response to Q#8) are sufficient to ensure that the generic enoxaparin product has the same active ingredient as Lovenox. FDA also evaluates impurities in the generic enoxaparin product, particularly with respect to their effect on immunogenicity. With the FDA approach, there is no scientific need to perform additional clinical studies to demonstrate equivalence of clinical effectiveness and safety of generic enoxaparin to Lovenox.

Although the EMA Guideline requires clinical studies to demonstrate comparable effectiveness to a similar LMWH, FDA notes that its approach (i.e., the five criteria) is more sensitive to differences between two enoxaparin products than the clinical studies recommended in the EMA guideline.

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