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{Part of Complete Approval Document 5226341A} Fragmin (Pharmacia and Upjohn) 03/30/1999 Supplemental Approval [Prophylaxis of Deep Vein Thrombosis]: S8 Approval Letter; Final Labeling

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-287/S-008

Pharmacia & Upjohn
Attention: James H. Chambers
7000 Portage Road
Kalamazoo, Michigan 49001-0199

MAR 30 1999

Dear Mr. Chambers:

Please refer to your supplemental new drug application dated April 16, 1997, received April 17, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Fragmin® (dalteparin sodium injection).

We acknowledge receipt of your submissions dated May 9, June 11 and 12, August 13, November 21, 1997, and February 25, March 19, September 8, and November 6, 1998. Your submission of November 6, 1998 constituted a complete response to our April 15, 1998 action letter.

This supplemental new drug application provides for the use of Fragmin® for prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism, in patients undergoing hip replacement surgery.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-287/S-008." Approval of this submission by FDA is not required before the labeling is used

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Karen Oliver, Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

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Lilia Talarico, M D.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Package Insert Text

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020287/S008

PRINTED LABELING

FRAGMIN®
dalteparin sodium injection

For *Subcutaneous* Use Only

SPINAL/EPIDURAL HEMATOMAS

When neuraxial anesthesia (epidural/spinal anesthesia) or spinal puncture is employed, patients anticoagulated or scheduled to be anticoagulated with low molecular weight heparins or heparinoids for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis

The risk of these events is increased by the use of indwelling epidural catheters for administration of analgesia or by the concomitant use of drugs affecting hemostasis such as non steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, or other anticoagulants The risk also appears to be increased by traumatic or repeated epidural or spinal puncture

Patients should be frequently monitored for signs and symptoms of neurological impairment If neurological compromise is noted, urgent treatment is necessary

The physician should consider the potential benefit versus risk before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis (also see WARNINGS, Hemorrhage and PRECAUTIONS, Drug Interactions)

DESCRIPTION

FRAGMIN Injection (dalteparin sodium injection) is a sterile, low molecular weight heparin It is available in single-dose, prefilled syringes and a multiple-dose vial With reference to the W H O First International Low Molecular Weight Heparin Reference Standard, each syringe contains 2500 (16 mg dalteparin sodium) or 5000 (32 mg dalteparin sodium) anti-Factor Xa international units (IU) in 0 2 mL Each 9 5 mL vial contains 10,000 (64 mg dalteparin sodium) anti-Factor Xa IU per 1 mL, for a total of 95,000 anti-Factor Xa IU per vial

Each prefilled syringe also contains Water for Injection and sodium chloride, when required, to maintain physiologic ionic strength The prefilled syringes are preservative free Each multiple-dose vial also contains Water for Injection and 14 mg of benzyl alcohol per mL as a preservative The pH of both formulations is 5 0 to 7 5

Dalteparin sodium is produced through controlled nitrous acid depolymerization of sodium heparin from porcine intestinal mucosa followed by a chromatographic purification process It is composed of strongly acidic sulphated polysaccharide chains (oligosaccharide, containing 2,5-anhydro-D-mannitol residues as end groups) with an average molecular weight of 5000 and about 90% of the material within the range 2000-9000 The molecular weight distribution is

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