DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

TRANSMITTED VIA FACSIMILE

JUL 20 2000

James L. Gaskill, R.Ph.
Associate Director, Regulatory Affairs
DuPont Pharmaceuticals Company
Chestnut Run Plaza, MR 2416
974 Centre Road
Wilmington, DE 19805

RE: NDA #20-484
Innohep (tinzaparin sodium injection)
MACMIS ID #9154

Dear Mr. Gaskill:

This letter concerns the dissemination of promotional labeling and advertising by DuPont Pharmaceuticals Company ("DuPont") for Innohep (tinzaparin sodium injection). The Division of Drug Marketing, Advertising, and Communications (DDMAC) has reviewed a Press Release for Innohep disseminated on July 18, 2000, as part of its monitoring program, and has concluded that DuPont is disseminating materials that lack fair balance and contain misleading promotional claims in violation of the Federal Food, Drug, and Cosmetic Act and implementing regulations. A description of our objections follows.

Lack of Fair Balance

The Press Release minimizes the serious risks associated with Innohep therapy by failing to include important risk information contained in the approved product labeling for Innohep. Specifically, the boxed and bolded warnings that: "Spinal or epidural hematoma can occur with the associated use of low molecular weight heparins or heparinoids and spinal/epidural anesthesia or spinal puncture which can result in long-term or permanent paralysis. The risk of these events is higher with the use of post-operative indwelling epidural catheters or with the concomitant use of additional drugs affecting hemostasis such as NSAIDs," is omitted. The bolded warning, "Innohep should not be used in patients with a history of heparin-induced thrombocytopenia," is also omitted, as are the contraindications in "patients with known hypersensitivities to

heparin, sulfites, benzyl alcohol, or pork products." The Press Release statement that "like other anticoagulants, Innohep should be used with caution in conditions with increased risk of hemorrhage," is not sufficient to provide the necessary risk information.

Also, the adverse event information that does appear in the Press Release is incomplete and does not fairly balance the promotional claims for Innohep. Specifically, the most common adverse events of injection site hematomas (16%), and abnormal elevations of AST (8.8%) and ALT (13%) are not included in the press release, nor is the incidence of urinary tract infection (3.7%) or pulmonary embolism/chest pain (2.3%).

Expanded Indication

The statement that "Innohep offers the advantage of being the only once-a-day heparin product for all patients with DVT," is false or misleading because it suggests that Innohep is indicated for use in all DVT patients, that it is approved for monotherapy, and that it is the only low molecular weight heparin that is administered once-a-day. However,

- the safety and efficacy of Innohep has not been studied in DVT outpatient populations.

- Innohep is not approved as monotherapy for the treatment of DVT patients. Its only approved used is in conjunction with the administration of warfarin sodium. The clinical trial that supported the approval of Innohep in DVT patients studied only patients on concomitant warfarin therapy.

- Innohep is not the only low molecular weight heparin (LMWH) that is approved for administration as a once-a-day treatment for DVT patients.

Misrepresentation of Clinical Data

The Press Release is misleading because it misrepresents the significance of clinical data from the double-blind clinical trial used for the basis of approval. The Press Release states that the total thromboembolic events (DVTs and/or PEs) were 2.8% in the Innohep treatment arm, as compared to 6.8% in the heparin treatment arm, with a thromboembolic event rate difference of 4.0%. However, the Press Release fails, to also state that the 90-day cumulative thromboembolic (TE) rate [recurrent DVT or PE] with Innohep was not significantly different than the rate with unfractionated heparin.

Requested Action

In order to address these objections, DDMAC requests that DuPont:

1. Immediately ceases further use of these and other materials and practices with the same or similar messages.

2. Provide DDMAC, in writing, with DuPont's intent to comply with the above. This response should include a list of all violative promotional materials and DuPont's methods for discontinuing their use.

DuPont's response should be received no later than July 31, 2000. If you have any questions, you should direct them to the undersigned in writing or by facsimile at (301) 594-6759 or at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-42, Rm. 17B-20, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds DuPont that only written communications are considered official. In all future correspondence regarding this particular matter, please refer to MACMIS ID #9154 in addition to the NDA number.

Sincerely,

Patricia Kuker Staub, R.Ph, J.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications

today's news

Dupont Pharmaceuticals' Innohep(R) Receives FDA Approval For the Treatment of Deep Vein Thrombosis

Website

Once-Daily Low Molecular Weight Heparin Product
Could Benefit Thousands of DVT Patients Each Year

WILMINGTON, Del., July 18 /PRNewswire/ -- DuPont Pharmaceuticals Company today announced that its once-daily low molecular weight heparin medication Innohep(R) (tinzaparin sodium injection) has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of acute symptomatic deep vein thrombosis (DVT) with or without pulmonary embolism when administered in conjunction with warfarin sodium. The safety and effectiveness of Innohep(R) were established in hospitalized patients.

DuPont Pharmaceuticals, a wholly owned independent subsidiary of DuPont (NYSE: DD), obtained the U.S. marketing rights for Innohep(R) from Leo Pharmaceutical Products, a Danish firm that markets the product in more than 20 countries outside the United States.

"We are very pleased with FDA's rapid 10-month initial review to approve Innohep(R)," said Nicholas L. Teti, president and chief executive officer of DuPont Pharmaceuticals. "Obtaining the approval of this important new low molecular weight heparin product demonstrates our commitment to anticoagulation patients and to on-going thrombosis research as part of our overall business strategy."

Venous thromboembolic disease, including DVT, is a common yet serious disorder that affects approximately five million Americans annually. It can lead to pulmonary embolism (PE), which develops in about 500,000 people each year and is fatal in almost 50,000 individuals annually. Acute DVT alone accounts for almost 800,000 hospitalizations each year.

The treatment of DVT -- with or without PE -- has, in recent years, been transformed by the use of low molecular weight heparins. Innohep(R) offers the advantage of being the only once-a-day low molecular weight heparin product for all patients with DVT.

In a double-blind clinical trial published in the New England Journal of Medicine that enrolled 435 patients with symptomatic proximal DVT (six percent had coexistent symptomatic PE), Innohep(R) was shown to be equivalent to standard heparin therapy in the prevention of recurrent venous thromboembolism (DVT and/or PE). Total thromboembolic events (DVTs and PEs) were six of 216 patients (2.8%) in the Innohep(R) treatment arm and 15 of 219 patients (6.8%) in the intravenous (I.V.) heparin treatment arm. The 95% confidence interval for the total thromboembolic event rate difference (4.0%) was 0.07%, 8.07%. Mortality with Innohep(R) was 4.6% (10 patients) and with heparin 9.6% (21 patients). The 95% confidence interval for the mortality difference was 0.16%, 9.76%.

The most common adverse event in controlled clinical trials evaluating Innohep(R) for DVT treatment was bleeding; however, the incidence of major bleeding was low (0.8% of 519 patients treated with subcutaneous Innohep(R) as compared to 2.7% of 524 patients treated with I.V. heparin). Other bleeding events (occurring at a frequency of greater than or equal to 1%) associated with Innohep(R) treatment were epistaxis (1.9%), hemorrhage (1.5%) and hematuria (1.0%). Like other anticoagulants, Innohep(R) should be used with caution in conditions with increased risk of hemorrhage.

DuPont Pharmaceuticals is a worldwide business that focuses on research, development, and delivery of pharmaceuticals and medical imaging products to treat unmet medical needs in the fights against HIV, cardiovascular disease, central nervous system disorders, cancer and inflammatory disease.

DuPont is a science company, delivering science-based solutions that make

a difference in people's lives in food and nutrition; health care; apparel; home and construction; electronics; and transportation. Founded in 1802, the company operates in 70 countries and has 94,000 employees.

For full Innohep(R) prescribing information, please visit the company's Web site at http://www.dupontpharma.com or call 1-800-4PHARMA (1-800-474-2762).

Innohep(R) is a registered trademark of Leo Pharmaceutical Products

SOURCE Dupont Pharmaceuticals Company
Web Site: http://www.dupontpharma.com

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