DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

David Cundiff, M.D.
319 Grand Avenue
Long Beach, California 90814

DEC 19 2001

Dear Dr. Cundiff:

We refer to your correspondence dated August 9, 2000 containing a copy of a review article titled, "Anticoagulation for Venous Thromboembolism" and the cover letter included in the submission of the article to the New England Journal of Medicine.

We also refer to our November 13, 2000 letter to you providing information in response to your communications.

Further, we refer to your most recent electronic mail communications with the Agency regarding previous and ongoing venous thromboembolic disease treatment studies and the review article by Paul Egermayer, M.D., entitled "The Effects of Heparin and Oral Anticoagulants on Thrombus Propagation and Prevention of the Postphlebitic Syndrome" (unpublished).

As was explained in the November 13, 2000 letter, heparin sodium injection was first approved on June 22, 1939 for prevention and treatment of postoperative thrombosis and embolism and re-review of the efficacy of the drug was conducted under the DES ("drug-efficacy study") and its implementation program following the Drug Amendments of 1962. The National Research Council of the National Academy of Sciences (NAS/NRS) concluded in 1970 that heparin was effective for the treatment and prevention of all venous and arterial thrombosis, thrombembolic disease, and the prevention and treatment of pulmonary embolism. The FDA evaluated and concurred with the NAS/NRS report.

Currently, heparin sodium injection is approved for the following indications: prophylaxis and treatment of venous thrombosis and its extension; in low-dose regimen for prevention of postoperative deep venous thrombosis and pulmonary embolism in patient undergoing major abdominothoracic surgery who are at risk for developing thromboembolic disease; for prophylaxis and treatment of pulmonary embolism; in atrial fibrillation with embolization; for diagnosis and treatment of acute and chronic consumptive coagulopathies (disseminated intravascular coagulation); for prevention of clotting in arterial and cardiac surgery, and for prophylaxis and treatment of peripheral arterial embolism. Heparin may also be employed as an anticoagulant in blood transfusions, extracorporeal circulation, dialysis procedures, and in blood samples for laboratory purposes.

Thrombus extension and embolization are well-recognized complications of proximal deep vein thromboses (DVT). Silent pulmonary emboli (PE) can be detected by lung scans in the majority of patients with DVT and 80 to 90 per cent of PE arise from proximal DVT. Pulmonary embolism is associated with high mortality and morbidity.

Early clinical trials showed reduction in mortality in patients with DVT/PE treated with heparin compared to untreated or placebo-treated patients (Barritt DW, Jordan SC. Lancet 1960, 1:130901312). Although the initial clinical trials of heparin were limited in size and not performed according to the current criteria and requirements of adequate and well-controlled design, they provided substantial evidence of efficacy. Over the years, numerous clinical trials have confirmed the efficacy and safety of heparin and other antithrombotic compounds for the treatment and prevention of thromboembolic events (TEE).

The clinical benefit of oral anticoagulants (Vit.K antagonists) provide further support for the benefit of anticoagulation in general. Prompt initiation and proper dosing of unfractionated heparin in the acute phase of DVT/PE reduce the risk of thrombus extension and embolization. Clinical trials have demonstrated that oral anticoagulant therapy must be started concomitantly or shortly after initiation of heparin and continued beyond the acute phase of DVT/PE in order to effectively reduce the risk of recurrence of thromboembolic events. Prospective, randomized studies have established the optimal intensity of anticoagulation with oral Vitamin K antagonists for patients with idiopathic DVT and the need of prolonged thromboprophylaxis for patients with high and persistent risk of TEEs. The effectiveness of warfarin has also been clearly demonstrated for prophylaxis of serious thromboembolic events, such as stroke, in atrial fibrillation and prosthetic heart valve.

Randomized, controlled clinical trials and meta-analyses of randomized trials that compared heparin to low molecular weight heparin (LMWH) indicate that LMWH is effective and safe for the initial management of DVT/PE, perhaps even more effective than unfractionated heparin. Notably, statistically significant reduction in mortality was detected in two meta-analyses that compared LMWH to unfractionated Heparin [1) Gould MK, Dembitzer AD, et al. Ann Intern Med 1999, May 18; 130, 10: 800-9, and 2) Dolovich LR, Ginsberg JS et al. Arch Intern Med, 2000, 160: 181-8]. Although these analyses obviously do not directly support heparin, they do provide further evidence that drugs with properties similar to heparin have favorable effects on survival.

The effectiveness of unfractionated heparin for primary thromboprophylaxis in patients undergoing general surgery at risk of thromboembolic complications has been demonstrated in placebo-controlled clinical trials. Subsequent clinical trials with low molecular weight heparins, heparinoids, and direct antithrombins have confirmed the

effectiveness of these compounds for primary thromboprophylaxis in patients at high risk due to general or orthopedic surgery or serious medical conditions. A placebo-controlled large clinical trial of a LMWH in patients undergoing general surgery showed a statistically significant reduction of total mortality and fatal PE in the LMWH-treated patients (Pezzuoli G et al. Hemostasis, 1990; 20 Suppl 1:193-204).

While it is recognized that control of coagulation is mediated via a complex system of factors and is characterized by a balance of opposing forces, the overall weight of the vast amount of clinical and scientific information available continues to support the safety and effectiveness of anticoagulants when used as labeled for primary thromboprophylaxis in patients at risk of TEE due to surgical procedures or other underlying predisposing conditions and, in patient with DVT/PE, to reduce the risk of thrombus extension, embolization and recurrent DVT/PE.

The Agency has carefully reviewed the data, and is satisfied with the quality and quantity of data available in support of the stated indication.

As with all FDA approved medicines, anticoagulation therapy continues to be under FDA oversight for safety via the post-marketing surveillance program (MEDWATCH).

This letter serves as the Agency's definitive comments to your communications.

Sincerely,

Lilia Talarico, M.D.
Division Director
Division of Gastrointestinal and Coagulation
Drug Products, HFD-180
Center for Drug Evaluation and Research

Robert J. Temple, M.D.
Associate Director for
Medical Policy
Center for Drug Evaluation
and Research