DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-345/S-004/S-005

Fonda B.V.
Attention: Ann Hards, Ph.D., Senior Director
Great Valley Parkway
P.O. Box 3026
Malvern, PA 19355

Dear Dr. Hards

Please refer to your supplemental new drug applications dated July 31, 2003, received July 31, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ARIXTRA® (fondaparinux sodium) Injection, 5.0 mg, 7.5 mg and 10.0 mg.

We acknowledge receipt of your submissions to S-004 dated September 5 and November 20, 2003; February 5, April 6, May 19, 24 and 28, 2004.

We also acknowledge receipt of your submissions to S-005 dated February 5, April 6, May 19, 24 and 28, 2004.

These supplemental new drug applications provide for the use of ARIXTRA (fondaparinux sodium) Injection for the treatment of acute deep vein thrombosis without pulmonary embolism when administered in conjunction with warfarin sodium and for the treatment of acute pulmonary embolism when administered in conjunction with warfarin sodium.

We completed our review of these applications, as amended. These applications are approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text and with the minor editorial revisions listed below and indicated in the enclosed labeling.

1. In the **CLINICAL STUDIES** section, Treatment of Deep Vein Thrombosis subsection, second paragraph, first sentence that begins "During the initial treatment period . . ." delete the word "of" after the word "endpoint" so that the sentence reads "During the initial treatment period, 18 (1.6%) of patients treated with fondaparinux sodium and 10 (0.9%) of patients treated with enoxaparin sodium had a VTE endpoint (95% CI for the treatment difference [fondaparinux sodium-enoxaparin sodium] for VTE rates: -0.2%; 1.7%)."

2. In the **CLINICAL STUDIES** section, Treatment of Pulmonary Embolism subsection, second paragraph, first sentence that begins "During the initial treatment period . . ." delete the word "of" after the word "endpoint" so that the sentence reads "During the initial treatment period, 12 (1.1%) of patients treated with fondaparinux sodium and 19 (1.7%) of patients treated with heparin had a VTE endpoint (95% CI for the treatment difference [fondaparinux sodium-heparin] for VTE rates: -1.6%; 0.4%)."

The final printed labeling (FPL) must be identical, and include the minor editorial revisions indicated, to the enclosed labeling (text for the package insert) and submitted labeling (package insert submitted May 28, 2004, immediate container and carton labels submitted July 31, 2003).

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 21-345/S-004, S-005." Approval of these submissions by FDA is not required before the labeling is used.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We are deferring submission of your pediatric studies for ages birth to 16 years years until May 31, 2009.

Your deferred pediatric studies required under section 2 of the Pediatric Research Equity Act (PREA) are considered required postmarketing study commitments. The status of these postmarketing studies shall be reported annually according to 21 CFR 314.81. These commitments are listed below.

1. Deferred pediatric study under PREA for the treatment of the treatment of acute deep vein thrombosis when administered in conjunction with warfarin sodium in pediatric patients ages birth to 16 years.

   Final Report Submission: May 31, 2009.

2. Deferred pediatric study under PREA for the treatment of the treatment of acute pulmonary embolism when administered in conjunction with warfarin sodium in pediatric patients ages birth to 16 years.

   Final Report Submission: May 31, 2009.

Submit final study reports to this NDA. For administrative purposes, all submissions related to these pediatric postmarketing study commitments must be clearly designated "**Required Pediatric Study Commitments**".

We remind you of your postmarketing study commitments in your submission dated May 28, 2004. These commitments are listed below.

1. Low Body Weight Patients (<50 kg)

   The clinical study report for study POP5108 "A repeated dose pharmacokinetic study in healthy volunteers to compare 1.5 mg of fondaparinux sodium in subjects with a low (35 to 50 kg) body weight to 2.5 mg of fondaparinux sodium in subjects with standard (60 to 100 kg) body weight"

Simulation data using POPPK analysis with modeling performed on patients undergoing VTE treatment and simulations performed on 50,000 subjects.

Protocol Submission: N/A
Study Start: N/A
Final Report Submission: within one month of the approval date of NDA 21-345 supplemental applications 004 and 005

2. Patients in Races Other Than Caucasian

Japanese
Pharmacokinetic comparison of Japanese and Caucasians from single-dose Phase I studies.

Black
POPPK analysis data from clinical study DRI2643 "A multicenter, randomized, parallel, double-blind, dose ranging study of subcutaneous Org31540 SR90107A with an assessor blind, comparative control group of subcutaneous LMWH in the prevention of deep vein thrombosis after elective total hip replacement", which includes data at the 6 and 8 mg dose;

Summary of the efficacy and major bleeding data in the DVT prophylaxis and VTE treatment submitted applications.

Protocol Submission: N/A
Study Start: N/A
Final Report Submission: within one month of the approval date of NDA 21-345 supplemental applications 004 and 005

3. Patients with Hepatic Impairment

The clinical study report for study 63132 "A phase I trial to evaluate and compare the safety, pharmacokinetics and pharmacodynamics of a single dose of 7.5 mg subcutaneous Org31540/SR90107A in subjects with moderate hepatic impairment and subjects with normal liver function"

Protocol Submission: N/A
Study Start: N/A
Final Report Submission: within one month of the approval date of NDA 21-345 supplemental applications 004 and 005

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "**Postmarketing Study Protocol**", "**Postmarketing Study Final Report**", or "**Postmarketing Study Correspondence**."

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Gastrointestinal and Coagulation Drug Products (HFD-180) and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410
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 reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Diane Moore, Regulatory Project Manager, at (301) 827-7476.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Gastrointestinal & Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Robert Justice

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