

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: 21-345

CORRESPONDENCE

MEMORANDUM OF TELECON

DATE: November 29, 2001

TIME: 2pm-3:30pm

APPLICATION NUMBER: NDA 21-345; Arixtra® (fondaparinux sodium) Injection

BETWEEN:

Name:

Sanofi-Synthelabo Inc.

Jean Bouthier, Clinical Development
Sophie Claudel, Biostatistics
Marc Cluzel, Product Development
Francois Donat, Clinical Pharmacokinetics and Metabolism
Richard Gural Regulatory Affairs,
Ann Hards, Regulatory Affairs
David Faunce, Regulatory Affairs

Organon Inc.

Ashok Didolkar, Regulatory Affairs
David Nicholson, Program Management

Phone: 610-889-8540

AND

Division of Gastrointestinal and Coagulation Drug Products, HFD-180

Victor Raczowski, M.D., M.Sc., Acting Division Director
Kathy Robie-Suh, M.D., Ph.D., Medical Team Leader, Hematology
Min Lu, M.D., Medical Reviewer
Karen Oliver, RN, MSN, Regulatory Health Project Manager

Division of Biopharmaceutics, DPE II, HFD-870

David Udo, Ph.D., Biopharmaceutics Reviewer

SUBJECT: Labeling Discussions

Regarding the proposed _____ CONTRAINIDICATIONS section of the package insert:

Agency

Regarding the _____

- Patients with moderate or severe renal impairment who received the drug experienced significant increased bleeding.
- The drug is given as a fixed dose (prefilled syringe without graduated markings) and there is not way to titrate the dose.
- The drug has a long half-life. Once the drug is administered, there no practical way to monitor the drug and there is no antidote for the drug.

Sponsor Response

- Based on the data, bleeding risks are minimized in the renally impaired patients if the drug is administered 6 hours after surgery.
- Re-iterated the dose regimen proposed in their August 31, 2001 submission for very elderly patients (≥ 75 years old) and/or with moderate or severe renal impairment (creatinine clearance $< \text{ml/min}$) and/or with low body weight ($< 50 \text{ kg}$). Specifically, the initial dosing "...6 hours following surgical closure" followed by an emphasis in the PRECAUTIONS section under Geriatric Use that the timing of the first dose (6 hrs: i.e., a 2 hour delay) required strict adherence.
- Referenced and discussed the information submitted August 31, 2001, pages 37-44.

Agency

- As per protocol, patients with severe renal impairment were excluded from the study.
- The proposed dosing regimen is based on a post-hoc, retrospective analysis of a very limited number of non-randomized patients in a selected subpopulation (moderate to severe renal impairment). The data should be considered hypothesis generating.
- Altering the timing of the initial dose may not provide a sufficient safety margin. Other considerations could include dose adjustment of the initial and subsequent doses.

- In addition to moderate and severe renal failure, the co-variants of age, weight, and gender need to be evaluated.

Sponsor Response

- The co-variants of age, weight, and gender have been identified as a “fragile” population, and given special consideration in the package insert in terms of timing of the fixed dose of the drug.
- Delaying the first post-operative dose (≥ 6 hrs following surgical closure) in “fragile” patients does not affect the efficacy of fondaparinux sodium 2.5 mg.

Agency

- Submit, via facsimile followed by hard copy, additional covariate analysis to support your position on “fragile” population including patients with renal impairment and the proposed dosing regimen.

Regarding the terms “active comparator” vs _____

Agency

- Comparative claims must be fair between the two agents.
- Concerned about the timing of the drugs given during the clinical trials: Arixtra 6 hours after surgery, and _____ 20 hours after surgery.
- _____ is not approved for the indications of hip fractures and “major knee surgery.”

Sponsor Response

- For the hip replacement surgery, _____ was dosed as prescribed in the package insert, i.e., 30 mg initiated 12-24 hours after surgery or 40 mg 12 hours before surgery.

The wording after Tables 1, 2, and 3 regarding the risk/benefit of the drug vs the comparator

Agency

- Wording provides a fair balance of risk/benefit for the two drugs.

Sponsor Response

- The wording is unnecessary and should be deleted. Arixtra has a superior safety and efficacy profile when compared to enoxaparin.

The sponsor agreed to submit the requested PK/PD data via facsimile. A follow-up, face-to-face meeting will be scheduled on Monday. The call was concluded.

Minutes Preparer:

Karen Oliver, RN, MSN
Regulatory Health Project Manager

Chair Concurrence:

Victor Raczkowski, M.D., M.Sc.
Acting Division Director

APPEARS THIS WAY
ON ORIGINAL

R/D init: V.Raczkowski 12/07/01
draft: KO/December 3, 2001
final: KO/12/07/01. _____

TELECON

APPEARS THIS WAY
ON ORIGINAL

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/s/

Victor Raczkowski
12/7/01 02:55:33 PM

APPEARS THIS WAY
ON ORIGINAL



NDA 21-345

Sanofi-Synthelabo Research
Attention: Richard P. Gural, Ph.D.
Vice President Regulatory Affairs
9 Great Valley Parkway
P.O. Box 3026
Malvern, PA 19355

Dear Dr. Gural:

We acknowledge receipt of your August 31, September 7, and October 9, 2001 resubmissions to your new drug application (NDA) for Arixtra[®] (fondaparinux sodium).

These resubmissions contain additional Chemistry, Manufacturing, and Controls, Clinical Pharmacology, Safety Data, and revised labeling (package insert, immediate container label, carton, and container tray label) information submitted in response to our August 15, 2001 action letter and the September 12, 2001 teleconference.

We consider this a complete class 1 response to our action letter. Therefore, the primary user fee goal date is December 9, 2001 and the secondary user fee goal date is February 9, 2002.

If you have any questions, call me at (301) 827-7457.

Sincerely,

{See appended electronic signature page}

Karen Oliver, RN, MSN
Regulatory Project Manager
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL



DEPARTMENT OF HEALTH & HUMAN SERVICES

Oliver

AUG 17 2001

Food and Drug Administration
Rockville MD 20857

P.H. Gebuhr, M.D.
Amager Hospital
Italiensvej 1
2300 Kobenhavn S, Denmark

Dear Dr. Gebuhr:

Between July 10 and July 13, 2001, Ms. Linda Leja and Dr. Susan Molchan, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol # 63118) of the investigational drug, fondaparinux sodium, trade name Xantidar TM, performed for Organon. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

We understand that your study was not conducted under an U.S. Investigational New Drug Application (IND). For your future reference, however, we offer our comments in the same manner as we would, had the study been performed in the U.S.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you did not adhere to all pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects. We note that at the conclusion of the inspection, Ms. Leja presented and discussed with you the item listed on Form FDA 483, Inspectional Observations. We observed that there were inconsistencies in the reporting of study drug administration between the source documents and case report forms for six subjects in the study (# 1389, 1773, 1740, 1733, 2035, and 1776).

We appreciate the cooperation shown Investigator Leja and Dr. Molchan during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/S/

John R. Martin, M.D.
Branch Chief
Good Clinical Practices I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, Maryland 20855



DEPARTMENT OF HEALTH & HUMAN SERVICES

Oliver

AUG 17

Food and Drug Administration
Rockville MD 20857

Dr. Z. Krska
VFN Praha, 1st Surgery Clinic
U nemocnice 2
12000 Praha 2, Czech Republic

Dear Dr. Krska:

Between July 16 and July 20, 2001, Ms. Linda Leja and Dr. Susan Molchan, representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (protocol # EFC2698) of the investigational drug fondaparinux sodium, trade name Xantidar, performed for Organon, NDA # 21-345. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you did adhere to all pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Leja and Dr. Molchan during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/S/

John R. Martin, M.D.
Branch Chief
Good Clinical Practices I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, Maryland 20855

**APPEARS THIS WAY
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

DISCIPLINE REVIEW LETTER

NDA 21-345

Fonda BV
C/O _____
Attention: Richard P. Gural, Ph.D.
Vice-President, Regulatory Affairs
9 Great Valley Parkway, P.O. Box 3026
Malvern, PA 19355

Dear Dr. Gural:

Please refer to your February 15, 2001 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for fondaparinux sodium injection.

Our review of the microbiology section of your submission is complete, and we have identified the following deficiencies. In order to correct these deficiencies:

[]

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final

decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Karen Oliver, Regulatory Project Manager, at (301) 827-7457.

Sincerely,

{See appended electronic signature page}

Julieann DuBeau, RN, MSN
Chief, Project Management Staff
Division of Gastrointestinal & Coagulation Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Brian Strongin
7/16/01 11:15:09 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

TRANSMITTED BY FACSIMILE

Kenneth R. Palmer
Associate Director, Drug Regulatory Affairs
Sanofi-Synthelabo Inc.
90 Park Avenue
New York, NY 10016

RE: NDA # 21-345
Arixtra (fondaparinux sodium injection)
MACMIS ID# 10122

Dear Mr. Palmer:

This letter responds to your June 7, 2001, request to the Division of Drug Marketing, Advertising, and Communications (DDMAC) for comments on the proposed representation of the proprietary and established names of Arixtra (fondaparinux sodium injection).

DDMAC, in consultation with the Division of Gastrointestinal and Coagulation Drug Products (DGCDP), has reviewed the proposed representation and offers the following comments. Please note that our comments relate solely to the representation of the names and do not in any way confer approval or acceptance of the proposed proprietary name, Arixtra.

The prominence of the established name is not commensurate with that of the proprietary name in your proposed representation. Factors used in determining prominence include typography, layout, contrast, and type size. The larger type size of, and contrast afforded to, the X in Arixtra detract from the prominence of the established name in the proposed representation. In addition, we are concerned that the presentation creates difficulty with recognition of the actual proprietary name and that this confusion may lead to medication errors. We recommend that you revise these elements to assure appropriate prominence for the established name and recognition of the proprietary name.

The relationship between the proprietary name and the established name should be clarified by the use of a phrase such as "brand of" preceding the established name, by brackets or parentheses surrounding the established name, or by other suitable means.

The representation should include quantitative ingredient information in direct conjunction with the display of the dosage form.

Palmer
Sanofi
NDA 21-345

Page 2

If you have any questions or comments, please contact me by facsimile at (301) 594-6771, 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 you that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS ID #10122 in addition to the NDA number.

Sincerely,

{See appended electronic signature page}

Margaret M. Kober
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

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/s/

Margaret Kober
6/28/01 01:50:04 PM

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DEPARTMENT OF HEALTH & HUMAN SERVICES

OLIVER

JUL - 3 2001

Food and Drug Administration
Rockville MD 20857

Philip C. Comp, M.D., Ph.D.
1111 N. Lee, Suite 543
Pasteur Building
Oklahoma City, Oklahoma 73103

Dear Dr. Comp:

Between June 20-22 and June 25-26, 2001, Mr. Lloyd D. Payne representing the Food and Drug Administration (FDA), met with you to review your conduct of a clinical study protocol # 095-002 of the investigational drug, fondaparinux sodium injection, trade name Xantidar, performed for NV Organon. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you did adhere to all pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Payne during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

(Handwritten signature)
/S/

John R. Martin, M.D.
Branch Chief
Good Clinical Practices I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, Maryland 20855

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DISCIPLINE REVIEW LETTER

NDA 21-345

Fonda BV
C/O _____
Attention: Richard P. Gural, Ph.D.
Vice-President, Regulatory Affairs
9 Great Valley Parkway, P.O. Box 3026
Malvern, PA 19355

Dear Dr. Gural:

Please refer to your February 15, 2001 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for fondaparinux sodium injection.

Our review of the Chemistry, Manufacturing and Controls section of your submission is complete, and we have identified the following deficiencies. In order to correct these deficiencies:

[]

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We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final

decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Karen Oliver, Regulatory Project Manager, at (301) 827-7457.

Sincerely,

{See appended electronic signature page}

Julieann DuBeau, RN, MSN
Chief, Project Management Staff
Division of Gastrointestinal & Coagulation Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Julieann DuBeau
6/26/01 11:54:38 AM

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-345

Fonda BV
C/O _____
Attention: Richard P. Gural, Ph.D.
Vice-President Regulatory Affairs
9 Great Valley Parkway, P.O. Box 3026
Malvern, PA 19355

Dear Dr. Gural:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xantidar™ (fondaparinux sodium injection).

We have completed our review of the proposed tradenames, "Xantidar", submitted to NDA 21-345, and "Arixtra", submitted to IND _____. The proposed tradename "Arixtra" is acceptable at this time.

The proposed proprietary name "Xantidar" is unacceptable due to the concerns regarding sound-alike, look-alike names that already exist in the U.S. marketplace including "Zanosar", "Zaditor", and "Fansidar".

If you have any questions, call Karen Oliver, Regulatory Project Manager, at (301)-827-7457.

Sincerely,

{See appended electronic signature page}

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

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/s/

Lilia Talarico
4/24/01 04:59:25 PM

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NDA 21-345

Fonda BV

C/O _____

Attention: Richard P. Gural, Ph.D.
Vice-President Regulatory Affairs
9 Great Valley Parkway, P.O. Box 3026
Malvern, PA 19355

Dear Dr. Gural:

Please refer to your pending February 15, 2001 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xantidar™ (fondaparinux sodium) Injection.

We also refer to our acknowledgment letter dated March 14, 2001, that stated the drug review priority classification for this application would be standard.

Upon further consideration of your application, we have concluded that this application should receive a priority review. The primary user fee goal date for this application is August 15, 2001.

If you have any questions, call Karen Oliver, Regulatory Project Manager, at (301) 827-7457.

Sincerely,

{See appended electronic signature page}

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

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/s/

Lilia Talarico
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-345

Fonda BV

C/O _____

Attention: Richard P. Gural, Ph.D.
Vice-President Regulatory Affairs
9 Great Valley Parkway, P.O. Box 3026
Malvern, PA 19355

Dear Dr. Gural:

We received your April 5, 2001 correspondence on April 6, 2001, requesting a meeting to discuss the rationale for requesting a priority review of the NDA. We considered your request and concluded that the meeting is unnecessary because the NDA will be a priority review.

If you disagree with our decision, you may discuss the matter with Karen Oliver, Regulatory Project Manager, at (301) 827-7457. If the issue cannot be resolved at the division level, you may formally request reconsideration according to our guidance for industry titled *Formal Dispute Resolution: Appeals Above the Division Level* (February 2000). The guidance can be found at <http://www.fda.gov/cder/guidance/2740fnl.htm>.

Sincerely,

{See appended electronic signature page}

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

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/s/

Lilia Talarico
4/24/01 04:33:36 PM



NDA 21-345

Fonda BV

C/O _____

Attention: Richard P. Gural, Ph.D.
Vice-President Regulatory Affairs
9 Great Valley Parkway, P.O. Box 3026
Malvern, PA 19355

Dear Dr. Gural:

Please refer to your pending February 15, 2001 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xantidar™ (fondaparinux sodium) Injection.

We also refer to our acknowledgment letter dated March 2, 2001, that stated the drug review priority classification for this application would be determined at the filing meeting.

Our policy regarding determination of priority or standard review status is based on the proposed indication and alternative treatments marketed for the proposed indication. We have determined that the drug will have a standard review status.

The primary user fee goal date for this application is December 15, 2001 and the secondary user fee goal date will be February 15, 2002.

If you have any questions, call Karen Oliver, Regulatory Project Manager, at (301) 827-7457.

Sincerely,

{See appended electronic signature page}

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

/s/

Lilia Talarico
3/14/01 02:02:52 PM



NDA 21-345

Fonda BV

c/o _____

Attention: Richard P. Gural, Ph.D.
Vice-President Regulatory Affairs
9 Great Valley Parkway, P.O. Box 3026
Malvern, PA 19355

Dear Dr. Gural:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Xantidar™ (fondaparinux sodium) Injection

Review Priority Classification: To be determined at the filing meeting.

Date of Application: February 15, 2001

Date of Receipt: February 15, 2001

Our Reference Number: NDA 21-345

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on April 16, 2001 in accordance with 21 CFR 314.101(a).

Be advised that, as of April 1, 1999, 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 (63 FR 66632). We acknowledge your January 16, 2001 correspondence submitted to IND _____ requesting a waiver for pediatric studies under 21 CFR 314.55 for Pentasaccharide Injection (Org 31540/SR 90107A). In a February 2, 2001 Agency letter, a waiver for pediatric studies for Pentasaccharide Injection (Org 31540/SR 90107A) was granted for the following indications: reducing the risk of venous thromboembolism in patients undergoing hip fracture surgery, hip replacement surgery, and major knee surgeries. We note in your February 15, 2001 NDA submission that the proposed tradename for Pentasaccharide Injection (Org 31540/SR90107A) is Xantidar™ (fondaparinux sodium) Injection.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Division Document Room, 6B-24
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-7457.

Sincerely,

{See appended electronic signature page}

Karen Oliver, RN, MSN
Regulatory Project Manager
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

**APPEARS THIS WAY
ON ORIGINAL**

/s/

Karen Oliver
3/2/01 11:09:47 AM

**APPEARS THIS WAY
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MEMORANDUM OF MEETING MINUTES

Meeting Date: December 5, 2001

Time: 11:30 am – 1 pm

Location: Parklawn Building, Maryland Conference Room

Application: NDA 21-345;
ARIXTRA (fondaparinux sodium injection)

Type of Meeting: Labeling Negotiations

Meeting Chair: Victor F. C.
Raczkowski, M.D., M.Sc.

Meeting Recorder: Karen Oliver, RN,
MSN

FDA Attendees, titles, and Office/Division:

Division of Gastrointestinal and Coagulation Drug Products, HFD-180

Victor Raczkowski, M.D., M.Sc., Acting Division Director

Kathy Robie-Suh, M.D., Ph.D., Medical Team Leader, Hematology

Min Lu, M.D., Medical Reviewer

Karen Oliver, Regulatory Health Project Manager

Division of Clinical Pharmacology and Biopharmaceutics, HFD-870

Suresh Doddapaneni, Ph.D., Biopharmaceutics Team Leader

David Udo, Ph.D., Biopharmaceutics Reviewer

Sam Haidal, Biopharmaceutics Reviewer

External Constituent Attendees and titles:

Sanofi-Synthelabo Inc.

Jean Bouthier, Clinical Development

Francois Donat, Clinical Pharmacokinetics and Metabolism

Richard Gural Regulatory Affairs,

Ann Hards, Regulatory Affairs

David Faunce, Regulatory Affairs

Eric Garrigow, Project Director

Organon Inc.

Ashok Didolkar, Regulatory Affairs

David Nicholson, Program Management

Background:

On February 15, 2001, Fonda BV (a joint venture between NV Organon and

Sanofi-Synthelabo SA) submitted an NDA for fondaparinux sodium injection for the following indication: "prevention of venous thromboembolic events in patients undergoing major orthopedic surgery of the lower limbs such as hip fracture, major knee or hip replacement surgeries". Fondaparinux sodium is provided in a prefilled, disposable syringe affixed with an automatic needle protection system as secondary packaging. Each prefilled syringe contained

2.5 mg fondaparinux sodium in 0.5 mL of an isotonic solution of sodium chloride and water for injection. Fondaparinux sodium, a single molecular entity, is a new anti-thrombotic agent obtained by chemical synthesis.

On August 15, 2001, an approvable letter was issued. On October 9, 2001, the sponsor submitted a full response to the action letter.

The Agency provided revised package insert labeling (red-line/strike-out version) to the sponsor on November 29, 2001 via facsimile. On November 29, 2001, the Agency and the sponsor discussed the revised package insert in a teleconference. On December 3, 2001, the Agency and sponsor continued their discussion of labeling issues in a face-to-face meeting. On December 5, 2002, at the request of the sponsor, a third meeting (face-to-face) was scheduled to discuss labeling issues. Based on the December 3, 2001 meeting, revised labeling was distributed to the sponsor at the start of the meeting.

Meeting Objectives:

Resolution of labeling issues.

Discussion Points (bullet format)

The revisions in the document were identified and discussed. The sponsor objected to several sections of the labeling. The sponsor's major objections are summarized as follows:

1. In the CLINICAL STUDIES section:

- o In each of the clinical trials discussion, the sentence: _____

- o In the "Hip Fracture" discussion, using the words "comparator drug" rather than _____
- o In each of the clinical trial discussions, the sentence: "Major bleeding episodes for both drugs are provided in Tables 4 and 5 (see **ADVERSE REACTIONS: Hemorrhage**)."
- o In each of the clinical trial discussions, the statement identifying factors that may have influenced the differences in efficacy and safety between ARIXTRA and the comparator/enoxaparin.
- o In each of the clinical trial tables, deleting a row entitled _____ with data.

1. In the CONTRAINDICATION section:

- o The moderate and severe renal failure contraindication.
- o The low body weight (<50 kg) contraindication.

NOTE: The sponsor would like information regarding moderate and severe renal failure to be described in the _____ section, in a subsection entitled "Renal Impairment Use".

1. In the DOSAGE AND ADMINISTRATION section:

[. . .]

At the conclusion of the meeting, the sponsor agreed to provide, via facsimile, in a timely manner, the following: (1) their revisions to the labeling sections discussed; and (2) a side-by-side comparison, preferably in table format, of the VTE rates and major bleeding events in pivotal clinical trial patients (listed by indication) with the moderate and severe renal failure. The Agency agreed to review their changes.

Minutes Preparer:

Karen Oliver, RN, MSN

Chair Concurrence:

Victor Raczkowski, M.D.,

M.Sc.

Drafted by: KO/December 6, 2001

Initialed by: V.Raczkowski

final: KO/12/06/01 _____

MEETING MINUTES

**APPEARS THIS WAY
ON ORIGINAL**

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

/s/

Victor Raczkowski
12/7/01 12:46:07 PM

**APPEARS THIS WAY
ON ORIGINAL**

REVIEW MANAGEMENT

PRIORITY REVIEW POLICY

CONTENTS

**PURPOSE
BACKGROUND
DEFINITIONS
POLICY
RESPONSIBILITIES AND PROCEDURES
EFFECTIVE DATE**

PURPOSE This MAPP describes the review priority classification of New Drug Applications (NDAs) and effectiveness supplements.

BACKGROUND

The NDA classification system provides a way of describing drug applications upon initial receipt and throughout the review process and prioritizing their review.

DEFINITIONS

Review Priority Classification. A determination that is made based on an estimate of its therapeutic preventive or diagnostic value. The designations "Priority" (P) and "Standard" (S) are mutually exclusive. Both original NDAs and effectiveness supplements receive a review priority classification but manufacturing supplements do not.

● **P -- Priority review ¹**

The drug product, if approved, would be a significant improvement compared to marketed products [approved (if such is required), including non-"drug" products/therapies] in the treatment, diagnosis, or prevention of a disease. Improvement can be demonstrated by, for example: (1) evidence of increased effectiveness in treatment, prevention, or diagnosis of disease; (2) elimination or

¹The CBER definition of a priority review is stricter than the definition that CDER uses. The biological drug, if approved, must be a significant improvement in the safety or effectiveness of the treatment diagnosis or prevention of a serious or life-threatening disease.

substantial reduction of a treatment-limiting drug reaction; (3) documented enhancement of patient compliance; or (4) evidence of safety and effectiveness of a new subpopulation.

- **S – Standard review**

All non-priority applications will be considered standard applications.

POLICY

- A “priority” designation is intended to direct overall attention and resources to the evaluation of applications for products that have the potential for providing significant preventative or diagnostic therapeutic advance as compared to “standard” applications.
- The priority determination does not take into consideration any information or estimate of price and is based on conditions and information available at the time the application is filed. It is not intended to predict a drug’s ultimate value or its eventual place in the market.
- Disputes in assigning review classifications should be handled in accord with MAPP 4040.1, “Appeals Process in Resolving Disputes over Applications in the Office of New Drug Evaluation” and 4040.2, “Scientific Reviews: Roles of Reviewers, Supervisors and Management; Resolution of Differences.”
- Because the review priority classification determines the review time frame the application receives, the review priority classification should be determined and assigned at the 45-day meeting if the application is to be filed.
- The final review classification of a new drug may change from “P” to “S” during the course of the review of a marketing application (NDA), either because of the approval of other agents or because of availability of new data; however, the review priority classification assigned at the time of filing will not change during the first review cycle and the user fee time frame of the original review cycle will be that based on the original priority.
- The review priority classification determines the overall approach to setting review priorities and user fee review time frames but is not intended to preclude work on other projects. It does not imply that staff working on a priority application cannot work on other projects, such as 30-day safety reviews of a newly submitted investigational new drug application (IND), preparation for end-of-phase 2 conferences, etc.
- Certain *ad hoc* special assignments may also take precedence. The supervisor is to advise the reviewer and team leader when an *ad hoc* assignment is to take precedence.

-
- As a general matter, if questions of priority arise, the reviewer should consult with the supervisor and team leader.
-

RESPONSIBILITIES AND PROCEDURES

Original Review Classification of NDAs and Efficacy Supplements

- **The Division Document Room (DDR) is responsible for:**
 1. upon receipt of an original NDA or efficacy supplement, forwarding the original copy of form FDA 2817, "NDA Assignment and Review Transmittal" to the appropriate medical group/team leader;
 2. after receipt of the completed transmittal form, entering the appropriate review priority classification on form FDA 2772, IND/NDA History Record, in box marked "Classification" and in the Center-wide Oracle-based Management Information System (COMIS) after assigned at the 45-day filing meeting.
- **The Medical Group Team Leader is responsible for:**
 1. determining the review priority classification of each efficacy supplement and NDA application at the 45-day filing meeting if the application is to be filed, after consulting, as needed, with the reviewing medical officer, supervisory chemist, pharmacologist, microbiologist and new drug division director;
 2. completing the appropriate box on the transmittal form;
 3. returning the completed transmittal form to the DDR.
- **Reviewers and Supervisors are responsible for:**

setting priorities of review related activities in accordance with this MAPP.
- **The Consumer Safety Officer (CSO)/Project Manager (PM) is responsible for:**

assuring that the correct classification codes are entered into the COMIS system.

Changes in classification at the end of the first cycle of review:

- **The Reviewing Medical Officer/Team Leader is responsible for:**
 1. recommending to the new drug division director any changes in classification justified on the basis of, for example, new information in an

IND or NDA, medical literature, advisory committee opinions or approval of a pharmacologically similar drug;

2. notifying the CSO/PM of the recommended change in classification.
- **The New Drug Division Director is responsible for:**
 1. approving or modifying the recommendation;
 2. notifying the CSO/PM of the change in classification.
 - **The Office Director is responsible for:**
 1. recommending changes in classification, if necessary;
 2. notifying the CSO/PM of the change in classification, if necessary.
 - **The CSO/PM is responsible for:**

notifying the DDR of the change in classification.
 - **The DDR is responsible for:**

changing the classification on form FDA 2772 and in COMIS.
-

EFFECTIVE DATE

This MAPP is effective upon date of publication.

Memorandum

To: Karen Oliver, Project Manager , HFD-180, Division of Gastrointestinal and Coagulation
Drug Products

From: Patricia Cricenti, Branch Chief , GHDB, DDIGD, HFZ-480 /S/

Through: Timothy A. Ulatowski, Director, DDIGD /S/ 7/4/01

Date: July 5, 2001

Re: Consult Review for NDA 21—Xantidar (fondaparinux sodium)

BACKGROUND

This consult was requested by CDER to evaluate the Sharps Injury Prevention Feature (SIPf-syringe) of a prefilled syringe that contains Xantidar (fondaparinux sodium). The drug will be indicated to reduce the risk of DVT in major orthopedic surgery.

SIMULATED USE STUDIES

GHDB had previously evaluated the protocol for the simulated studies as Pre I000166. The firm based their protocols on CDRH guidance document Supplementary Guidance on the Content of Premarket Notification [510(k)] Submissions for Medical Devices with Sharps Injury Prevention Features.

The firm has done two simulated studies to evaluate the sharps injury prevention for the prefilled syringe. One study was done with 68 healthcare workers using a total of 500 syringes. The other study was conducted with 100 consumers whose age was greater than 55 also evaluated a total of 500 syringes. Both studies were conducted using the same directions for use. Comments from the evaluator were provided and most comments were directed at the difficulty in removing the needle guard cap prior to the injection. The results of both simulated studies were acceptable demonstrating that the user was able to follow the directions for use and use the device without incurring a sharps injury.

LABELING:

The following are my comments regarding the labeling (instructions for use):

1. It is unclear to whom the directions for use in the labeling are directed. As it appears that the drug may be administered by healthcare workers, caretakers or the patient.
2. The hands in the section labeled instructions for use are not gloved.
3. The instructions for use do not mention wiping the skin with an alcohol wipe.
4. A diagram or sketch of the body sites available for injection should be provided.

5. The instructions for use that were used in the simulated use studies Appendix 1 (pages 5/7 to 7/7) are more detailed and describe each step of use. These should be used in the drug labeling.
6. I have attached the directions for use from the simulated studies with my suggestions.

RECOMMENDATION/CONCLUSION The results of the two simulated studies to evaluate the sharps injury prevention feature are acceptable and are consistent with the CDRH guidance document therefore GHDB has no further concerns with the sharps injury prevention feature of the prefilled syringe. The labeling issues listed above need to be addressed.

**APPEARS THIS WAY
ON ORIGINAL**

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Draft

Labeling

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

Division/Office: CDRH, HFZ-480
ATTENTION: Patricia Cricenti, Supervisor Microbiologist

FROM: HFD-180 (Division of Gastrointestinal and Coagulation Drug Products) Phone # 827-7457

DATE: 03/22/01	IND NO.:	NDA NO.: 21-345	TYPE OF DOCUMENT : NEW NDA	DATE OF DOCUMENT Submitted Feb 15, 2001
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NAME OF DRUG: Xantidar (fondaparinux sodium) Injection	PRIORITY CONSIDERATION: Priority??	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE: User fee Due Date: PRIORITY: DUE DATE August 15, 2001
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NAME OF FIRM: Fonda BV

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

- | | |
|--|---|
| STATISTICAL EVALUATION BRANCH | STATISTICAL APPLICATION BRANCH |
| <input type="checkbox"/> PE A OR B NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER: |
| <input type="checkbox"/> OTHER: | |

III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RICK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: NDA provides for reduction of risk of DVT in major orthopedic surgery of the lower limb. On March 21, 2001, I consulted (1) volume containing information on the "Sharps Injury Prevention feature (SIPf-syringe). At this time I am consulting (1) red notebook containing the "Use Studies" for this device. This device has NOT been cleared for marketing prior to the submission of the NDA, and was NOT used in the pivotal clinical trials for this application. Please evaluate this additional information. Dr. Ali-Al-Hakim is the review chemist. Thanks, Karen Oliver, Project Manager, 7-7457

NATURE OF REQUESTER:

METHOD OF DELIVERY (Check one):

X MAIL

HAND

SIGNATURE OF RECEIVER:

SIGNATURE OF DELIVERER:

/s/

Karen Oliver

3/22/01 03:16:32 PM

**APPEARS THIS WAY
ON ORIGINAL**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND _____

Sanofi-Synthelabo Inc.
Attention: David Faunce
9 Great Valley Parkway
P.O. Box 3026
Malvern, PA 19355

Dear Mr. Faunce:

Reference is made to your correspondence dated January 16, 2001, requesting a waiver for pediatric studies under 21 CFR 314.55.

We have reviewed the information you have submitted and agree that a waiver is justified for Pentasaccharide Injection (Org31540/SR90107A) for the following indications: reducing the risk of venous thromboembolism in patients undergoing hip fracture surgery, hip replacement surgery, and major knee surgeries.

Accordingly, a waiver for pediatric studies for this application is granted under 21 CFR 314.55 at this time.

If you have questions, please contact Karen Oliver, Regulatory Project Manager, at (301)-827-7457.

Sincerely,

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

/s/

Lilia Talarico
2/2/01 11:31:47 AM

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

(Division/Office): Microbiology, HFD-160
ATTENTION: Dr. Peter Cooney, Team Leader

FROM: HFD-180 (Division of Gastrointestinal and Coagulation Drug Products) Phone # 827-7457

DATE: 07/26/01	IND NO.:	NDA NO.: NDA 21-345	TYPE OF DOCUMENT :	DATE OF DOCUMENT 07-25-01
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NAME OF DRUG: Arixtra (fondaparinux sodium Injection)	PRIORITY CONSIDERATION: Standard	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE: User fee Due Date: AUGUST 15, 2001!!!!
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NAME OF FIRM: Fonda BV

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- TYPE A OR B NDA REVIEW
 END OF PHASE II MEETING
 CONTROLLED STUDIES
 PROTOCOL REVIEW
 OTHER:

- CHEMISTRY REVIEW
 PHARMACOLOGY
 BIOPHARMACEUTICS
 OTHER:

III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RICK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: I am consulting one volume. The submission contains the sponsor's response to the micro discipline review letter dated July 16, 2001. **PLEASE REVIEW ASAP or notify me that you will not be able to review the submission in this review cycle.** The due date is August 15, 2001!!!!. The chemistry reviewer is Dr. Ali Al-Hakim. Thanks, Karen Oliver, Project Manager

SIGNATURE OF REQUESTER:

METHOD OF DELIVERY (Check one):

MAIL

HAND

SIGNATURE OF RECEIVER:

SIGNATURE OF DELIVERER:

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

/s/

Karen Oliver

7/26/01 05:47:07 PM

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
(Division/Office): Microbiology, HFD-160 ATTENTION: Dr. Peter Cooney, Team Leader		FROM: HFD-180 (Division of Gastrointestinal and Coagulation Drug Products) Phone # 827-7457		
DATE: 02/27/01	IND NO.:	NDA NO.: NDA 21-345	TYPE OF DOCUMENT :	DATE OF DOCUMENT 02-15-01
NAME OF DRUG: Xantidar (fondaparinux sodium) Injection	PRIORITY CONSIDERATION: Standard	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE: User fee Due Date: 10 mo: Dec. 15, 2001 12mo: Feb. 15, 2002	
NAME OF FIRM: Fonda BV				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
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III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RICK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: New NDA-ELECTRONIC SUBMISSION. The network path location is: _____ I am consulting (1) volume that contains table of contents and summary information. Although the sponsor states that microbiology is "NA", please review appropriate data in the "chemistry" portion of the submission. This is a sterile product. If you have difficulty locating the submission in the EDR, please call me. The chemistry reviewer is Dr. Ali Al-Hakim. Thanks, Karen Oliver, Project Manager				
NATURE OF REQUESTER:		METHOD OF DELIVERY (Check one): <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> HAND		
SIGNATURE OF RECEIVER:		SIGNATURE OF DELIVERER:		

/s/

Karen Oliver
2/27/01 03:40:49 PM

**APPEARS THIS WAY
ON ORIGINAL**

Comments on NDA 21-345 Arixtra (fonaparinux sodium) 12/06/01
From A. Jacobs /S/121601

My previous comments have been addressed.

APPEARS THIS WAY
ON ORIGINAL

Comments on NDA 21-345 Arixtra (fonaparinux sodium) 7/27/01
From A. Jacobs

IS!

I have reviewed the pharm/tox review and labeling for this NDA.

I have spoken to Dr. Jasti Choudary about some minor revisions to the labeling, and he will address them.

1. Under carcinogenesis, mutagenesis, impairment of fertility, the spelling of chromosomal should be corrected.
2. Under pregnancy, reproduction studies could be better identified

**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: December 7, 2001
FROM: Florence Houn MD MPH
SUBJECT: Office Director Memo
TO: NDA 21-345 fondaparinux sodium (ARIXTRA Injection by Fonda BV)

This memo documents my concurrence with the Division of Gastrointestinal and Coagulation Drug Product's recommendation for marketing approval of fondaparinux sodium. The indications are for prophylaxis of deep vein thrombosis (DVT) which may lead to pulmonary embolism in patients undergoing hip fracture surgery, hip replacement surgery, and knee replacement surgery. Efficacy for this drug has been demonstrated in active control trials using enoxaparin. The safety database contained over 5,000 patients and showed no unexpected signal except bleeding risk being increased in certain subpopulations. The drug is administered by an injector device that was reviewed by the Center for Devices and Radiological Health and found to be acceptable. This device, however, limits the flexibility of dosing such that the entire aliquot of drug is delivered to the patient. Issues with this drug centered around: unfair comparisons for efficacy and safety, the sponsor's desire for an indication for prophylaxis in major knee surgery, and safety pertaining to hemorrhage. The division director's memo and the review memos well summarize these and other issues.

Unfair Comparison

The manufacturer felt strongly the studies demonstrated superiority of ARIXTRA compared to enoxaparin. However, the issues below outline FDA's rationale that superiority was not demonstrated.

The hip fracture trial (EFC2698) utilized 40mg of enoxaparin subcutaneously daily beginning 18 hours after surgery compared to 2.5mg of ARIXTRA subcutaneously daily beginning 6 hours after surgery.

The hip replacement studies have two concerns. Study EFC2442 did not reveal a result statistically different from the comparator. Study 63118 had a regimen of 2.5mg SQ beginning 6 hours after surgery versus enoxaparin 40 mg SQ daily beginning 12 hours before surgery. Only 88% of subjects received enoxaparin pre-operatively and the mean time between the last active pre-operative injection and start of surgery was 13 ± 14 hours. The approved labeling for enoxaparin states a dose of 40 given daily SQ starting 12 ± 3 hours before surgery may be considered. The labeling does mention enoxaparin by name because it is approved for this indication. It also states that the differences in safety and efficacy between ARIXTRA and enoxaparin may be due to differences as to when the initial dose was given. It is not known when the optimal timing of enoxaparin should be given such that a superiority claim for VTE prevention is not appropriate.

The knee replacement study used a regimen of 2.5 mg of ARIXTRA SQ daily beginning 6 hours after surgery versus 30mg enoxaparin twice a day starting at day 2. The average time in the trial for administering enoxaparin was 21 hours ± 2 hours. The label for enoxaparin for knee replacement DVT prophylaxis states 30 mg should be given SQ 12-24 hours after surgery. This dosing was still within the

labeled dosing times, but at the longer end. Again, enoxaparin optimal timing for prevention of VTE is unknown.

The issue of timing of initial drug also affects safety. The presence of more major bleeding with ARIXTRA with less VTEs may be because of timing of drug administration compared to enoxaparin. The manufacturer had wanted a superiority claim, but the outcome is not clearly superior (lower VTE rates but higher bleeding compared to enoxaparin does not necessarily make it a superior drug for risk/benefit). Nevertheless, overall the safety events (VTE and major bleeding) with this drug in the trials performed support approval.

Major Knee Surgery

Study 095-002 involved patient undergoing major knee surgery. However, on FDA review of a sample of records, all patients were knee replacement and the sponsor was not able to provide stratification based on type of knee surgery. They did indicate that patellar surgery was included, but were unable to provide percentages of this type and other types. Given our review of the cases, the study contained an overwhelming number of knee replacement surgeries and the evidence to support efficacy is for this indication.

Safety Pertaining to Major Bleeding, Especially in Subpopulations

There was more major bleeding in the ARIXTRA group (2.7%) than in the enoxaparin group (1.9%). There is no antidote for ARIXTRA. The half-life is long. There is no widely available tool to measure drug effect. The manufacturer strongly felt that ARIXTRA safety is similar to enoxaparin. They also felt that there should not be contraindications for moderate renal patients (they agree with severe renal impairment being a contraindication). They met face-to-face with the division 12-3-01 and 12-5-01 trying to convince the division their post-hoc analyses demonstrate that provision of the full drug dose (by injector, which does not allow partial dosing) can be given at 6 hours or greater with less bleeding for moderately impaired renal patients. The biopharm data were not rigorously collected specifically and prospectively to demonstrate maximum safe timing of dosing for these types of patients, however. The division felt that moderately impaired renal patients should be warned about increased bleeding and has placed such a statement in the warnings section. The labeling states the drug should be given between 6-8 hours and that administration less than 6 hours after surgery may increase risk of bleeding. The labeling includes statements about the lack of antidote, the lack of monitoring available for this drug, inability to switch unit-for-unit with other anticoagulant drugs, and risk factors associated with major bleeding.

The medical reviews clearly document that there is a dose-bleeding response curve such that moderate renal insufficiency resulted in 3.8% of patients with major bleeding. There is also a clear increased risk of major hemorrhage in patients weighing less than 50 kg. The company _____ 2.5mg to avoid bleeding in greater than 3% of patients. The company argued that these moderate renal impaired patients and lower weight patients are more at risk for DVT and could benefit from their drug. I discussed my view with the division director that the indications for efficacy are, in fact, safety endpoints (prevention of VTEs) and that one approach is to look at total major safety performance with respect to VTEs and major bleeding. On December 5, 2001 data was requested to look at VTE and major bleeding by renal function. These data were received on December 7, 2001 and showed that for these two safety events compared to enoxaparin.

	%VTE	and	%Major Bleed for ARIXTRA vs. enoxaparin
Normal Renal	- 50%		+64%
Mild Renal	-57%		+55%
Moderate Renal	-53%		+34%
Severe Renal	-27%		+103%

It must be noted that the number of actual cases of VTE are greater than major bleeding, a fact that figures into the overall public health impact of the drug. All other disciplines recommend approval. There is one phase 4 commitment for a biopharm study of the drug in hepatic impairment patients. All other issues being resolved, the drug has adequate safety and efficacy evidence for approval.

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Florence Houn
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