CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-345

CHEMISTRY REVIEW(S)
NDA 21-345

ARIXTRA (fondaparinux sodium Injection), 2.5 mg/0.5 mL

CHEMISTRY DIVISION DIRECTOR REVIEW

Applicant: Fonda BV
[Joint venture Between NV Organon and Sanofi BV]

Indication: Prophylaxis of DVT following hip and knee replacement and hip fracture

Presentations: Pre-filled Syringe w/ needle guard, and vials

EER Status: Acceptable 10/11/2001

Consults: CDRH – acceptable w/ labeling comments 7/19/2001
Microbiology – acceptable 7/31/20001
OPDRA – Arixtra OK, Xantidar no acceptable 10/29/2001
– confirmed 1011/2001

The drug substance is manufactured by Sanofi-Synthelabo Notre Dame Dedondville, France – The synthesis is
The was reviewed in 3 cycles, and issues related to characterization, impurities, specifications for intermediates and the drug substance, stability (24 month re-test), clarifying and upgrading manufacturing processes were satisfactorily resolved. Drug Substance is also manufactured by
The synthesis processes are identical to that done by Sanofi-Synthelabo. The was also reviewed in 3 cycles.

Discussion
The process is a synthetic “tour de force”. The drug substances have been demonstrated to be equivalent structurally, and to have the same impurity profile. The specifications for intermediates and the drug substance are adequate, however there may be the need to re-visit some specification after scale-up.

Conclusion
Drug substance manufacturing and controls are satisfactory.

The drug product is a solution provided as 2.5 mg / 0.5 mL fill syringe cartridges with needle guard. Product will be manufactured at Sanofi-Chimie Synthelabo Notre Dame Dedondville, France. All container/closure components were reviewed under DMFs and were found acceptable. The manufacturing process is
The formulation is an aqueous solution with added NaCl
The specification was found to be adequate following tightening of
impurities limits. The firm agreed to consider tightening impurities limits after experience has been gained in commercial production. Based upon structural considerations the firm was asked to assess anti-coagulant activity of certain impurities. Note that one of the impurities for which the limits were tightened was shown to have anti Xa activity. Stability data were provided to support a 24 month expiry.

Manufacturing is acceptable from a sterility assurance perspective.

The container, carton and insert labeling was found to be acceptable following minor revisions.

**Discussion**
The drug product manufacturing is well controlled, and the specification and labeling are acceptable.

**Conclusion**
The drug product manufacturing is acceptable.

**Over-All Conclusion**
From a CMC perspective the application is recommended for approval

/S/

12/6/01

Eric P Duffy, PhD
Director, DNDC II/ONDC
DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-345  REVIEW #: 3  DATE REVIEWED: 11/01/01

SUBMISSION TYPE  DOCUMENT DATE  CDER DATE  ASSIGNED DATE
Amendment  August 31, 2001  September 04, 2001  September 05, 2001

NAME & ADDRESS OF APPLICANT:
DRUG PRODUCT NAME
Fonda BV
Tripolis 300
Burgerweeshospad 311
1076 HS Amsterdam, The Netherlands

Proprietary:

Established:  Arixtra®

Code Name / #:  Fondaparinux

Chem. Type/Ther. Class:  Org31540/SR90107A

PHARMACOL. CATEGORY/INDICATION:
Prophylaxis of Deep Venous Thrombosis

DOSAGE FORM:

STRENGTHS:

ROUTE OF ADMINISTRATION:

Rx/OTC:

SPECIAL PRODUCTS:

Solution

2.5 mg/0.5 mL

Injection

✓ Rx  ___ OTC

___ Yes  ✓ No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,
MOLECULAR WEIGHT:


Molecular Weight: 1728
Molecular Formula: C₉₁H₄₃N₃Na₁₀O₉₁S₈
### SUPPORTING DMF DOCUMENTS:

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<th>Holder</th>
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### RELATED DOCUMENTS (if applicable):

- Biopharmaceutics
- Microbiology
- CDRH (Delivery Device)
- Office of Post-Marketing Drug Risk Assessment
  (Acceptable Proprietary Name: Aritra ®)
- Establishment Evaluation Reports

### Status

- Adequate
- Completed
- Acceptable
REMARKS
This review deals with amendment dated August 31, 2001 which contains responses to our IR
letter sent to the firm on August 15, 2001.
Comments regarding any unresolved chemistry related issues in the label insert will be conveyed
to the applicant by the project manager.

CONCLUSIONS & RECOMMENDATIONS:
The application may be approved from the Chemistry, Manufacturing and Control point of view.

Ali Al-Hakim, Review Chemist

Liang Zhou, Chemistry Team Leader

cc:
Org. NDA 21-345
HFD-180/Division File
HFD-180/V.Raczkowski
HFD-180/A.Al-Hakim
HFD-180/K.Oliver
HFD-180/Li. Zhōu
HFD-820/Directors
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/s/
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Ali Al-Hakim
11/1/01 12:02:28 PM
CHEMIST

Liang Zhou
11/1/01 01:39:09 PM
CHEMIST

APPEARS THIS WAY
ON ORIGINAL
DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-345  REVIEW #: 2  DATE REVIEWED: 08/06/01

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NAME & ADDRESS OF APPLICANT:
Fonda BV
Tripolis 300
Burgerweeshospad 311
1076 HS Amsterdam, The Netherlands

Proprietary: Arixtra™
Established: Fondaparinux
Code Name / #: Org31540/SR90107A
Chem. Type/Ther. Class: 1/P

PHARMACOL. CATEGORY/INDICATION:
Prophylaxis of Deep Venous Thrombosis

DOSAGE FORM:
Solution

STRENGTHS:
2.5 mg/0.5 mL

ROUTE OF ADMINISTRATION:
Injection

Rx/OTC:
✓ Rx  __ OTC

SPECIAL PRODUCTS:
__ Yes  ✓ No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Molecular Weight: 1728
Molecular Formula: C_{31}H_{43}N_{3}Na_{10}O_{49}S_{8}
Consults:

- Biopharmaceutics
- Microbiology
- CDRH (Delivery Device)
- Office of Post-Marketing Drug Risk Assessment

Completed (4/20/01). The office did not recommend the use of the propriety name “Xantidar”. However, OPDRA has no objection to the use of the name “Arixtra”. Therefore, firm decided to use the name Arixtra as the trade name. See OPDRA report dated April 20, 2001.

- Establishment Evaluation Reports. As of July 23, 2001, the following sites are pending:

  [ ]

  [ ]

  (Summary of the EER report is included at the end of this review)
REMARKS
This review deals with amendment dated 20 July 2001 which contains responses to our IR letter sent to the firm on June 26, 2001.

CONCLUSIONS & RECOMMENDATIONS:
Although the NDA holder provided satisfactory responses to most of our queries, however, the application remains approvable because the holder did not provide satisfactory and complete responses to the degradation product issues. These issues are delineated in the draft deficiency letter at the end of this review.
- The EER is till pending for two sites
- DMFs are deficient

Ali Al-Hakim, Review Chemist

Liang Zhou, Chemistry Team Leader

cc:
Org. NDA 21-345
HFD-180/Division File
HFD-180/L. Talarico
HFD-180/A. Al-Hakim
HFD-180/K. Oliver
HFD-180/Li. Zhou
HFD-820/Directors
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/s/
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Ali Al-Hakim
8/6/01 01:15:38 PM
CHEMIST

Liang Zhou
8/6/01 01:20:25 PM
CHEMIST

APPEARS THIS WAY
ON ORIGINAL
DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-345 REVIEW #: 1 DATE REVIEWED: 06/15/01

SUBMISSION TYPE DOCUMENT DATE CDER DATE ASSIGNED DATE

NAME & ADDRESS OF APPLICANT:
Fonda BV
Tripolis 300
Burgerweeshospad 311
1076 HS Amsterdam, The Netherlands

DRUG PRODUCT NAME
Arixtra™

Proprietary:
Established:
Code Name/ID:
Chemical/Ther. Class:
Org31540/SR90107A
I/P

PHARMACOL. CATEGORY/INDICATION:
Prophylaxis of Deep Venous Thrombosis

DOSAGE FORM: Solution
STRENGTHS:
2.5 mg/0.5 mL

ROUTE OF ADMINISTRATION:
Injection

Rx/OTC: \( \checkmark \) Rx ___ OTC

SPECIAL PRODUCTS:

\( \checkmark \) Yes \( \checkmark \) No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
\[ \alpha-D-glucopyranoside, \text{ methyl O-2-deoxy-6-O-sulfo-2-(sulfoamino)-}\alpha-D-glucopyranosyl-(1\rightarrow4)-O-\beta-D-glucopyranuronosyl-(1\rightarrow4)-O-2-deoxy-3,6-di-O-sulfo-2-(sulfoamino)-\alpha-D-glucopyranosyl-(1\rightarrow4)-O-2-O-sulfo-\alpha-L-idopyranuronosyl-(1\rightarrow4)-2-deoxy-2-(sulfoamino), \text{ 6- (hydrogen sulfate), decasodium salt.} \]

Molecular Weight: 1728
Molecular Formula: \( C_{31}H_{43}N_3Na_10O_{49}S_8 \)
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### RELATED DOCUMENTS (if applicable):

**Consults:**
- Biometrics
- Biopharmaceutics
- Microbiology
- CDRH (Delivery Device)
- Office of Post-Marketing Drug Risk Assessment (OPDRA) - February 15, 2001
  - The office does not recommend the use of the proprietary name “Xantidar”. However, OPDRA has no objection to the use of the name “Arixtra”. See OPDRA report dated April 20, 2001.
- Establishment Evaluation Report - March 05, 2001

**Remarks:**
The drug substance is manufactured used at different sites (and Sanofi-Chimie), however, the drug product commercial batches are manufactured by Sanofi-chimie site.
NDA 21-345

CONCLUSIONS & RECOMMENDATIONS:
The NDA is Approvable from the Chemistry, Manufacturing and Controls point of view. The NDA applicant should provide additional information delineated in the draft deficiency letter.

Ali Al-Hakim, Review Chemist

Linag Zhou, Chemistry Team Leader

cc:
Org. NDA 21-345
HFD-180/Division File
HFD-180/A.Ali-Hakim
HFD-180/K.Oliver
HFD-180/Li. Zhou
HFD-820/Directors
R/D Init by:

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/s/
Ali Al-Hakim
6/22/01 04:04:44 PM
CHEMIST

Liang Zhou
6/22/01 04:10:05 PM
CHEMIST
This is P-Drug.

Appears this way on original