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 – [redacted] The synthesis is [redacted]
The [redacted] 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 [redacted]
The synthesis processes are identical to that done by Sanofi-Synthelabo. The [redacted] 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 [redacted] 2.5 mg / 0.5 mL [redacted] 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 [redacted] The formulation is an aqueous solution with added NaCl [redacted] 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 reccomended for approval

/S/ 12/6/01

Eric P Duffy, PhD
Director, DNDC II/ONDC

APPEARS THIS WAY
ON ORIGINAL

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: Fonda BV

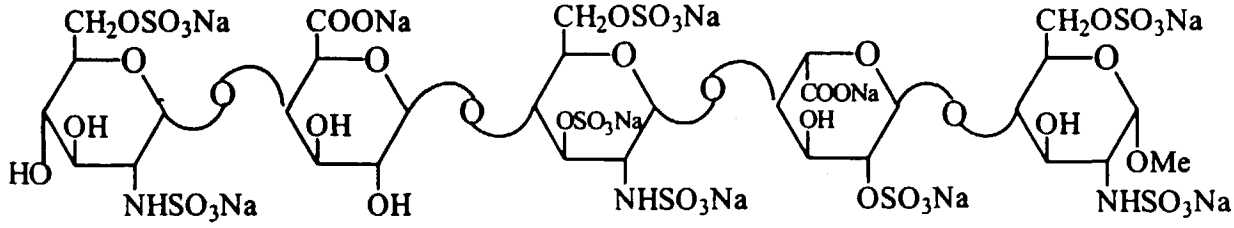
DRUG PRODUCT NAME

Tripolis 300
Burgerweeshispad 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:

α-D-glucopyranoside, methyl O-2-deoxy-6-O-sulfo-2-(sulfoamino)-α-D-glucopyranosyl-(1→4)-O-β-D-glucopyranuronosyl-(1→4)-O-2-deoxy-3,6-di-O-sulfo-2-(sulfoamino)-α-D-glucopyranosyl-(1→4)-O-2-O-sulfo-α-L-idopyranuronosyl-(1→4)-2-deoxy-2-(sulfoamino)-, 6-(hydrogen sulfate), decasodium salt.



Molecular Weight: 1728
Molecular Formula: $C_{31}\ H_{43}\ N_3\ Na_{10}\ O_{49}\ S_8$

SUPPORTING DMF DOCUMENTS:

Type/ Number	Subject	Holder	Status	Reviewer and review date	Authorization Letter Date
II	Drug Substance		Adequate	Ali Al-Hakim HFD-180 10/14/01	02/05/2001
II	Drug substance	Sanofi-Synthelabo	Adequate	Ali Al-Hakim HFD-180 10/14/01	12/04/2001
III			Adequate	R.Harapanhalli HFD-160 08/17/00	12/04/2000
III			Information regarding is provided in he NDA	Information is satisfactory	12/05/2000
III	Stopper;		Adequate	R.Harapanhalli HFD-160 08/23/2000	11/20/2000
III			Adequate Information is provided in the NDA	Veterinary Med. 08/03/2000 Information is satisfactory	12/05/2000 12/05/2000

RELATED DOCUMENTS (if applicable): IND

Consults: **Status**

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

APPEARS THIS WAY
ON ORIGINAL

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. Zhou
HFD-820/Directors

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/s/

Ali Al-Hakim
11/1/01 12:02:28 PM
CHEMIST

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

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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**

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Amendment	July 20, 2001	July 23, 2001	July 23, 2001

NAME & ADDRESS OF APPLICANT: Fonda BV

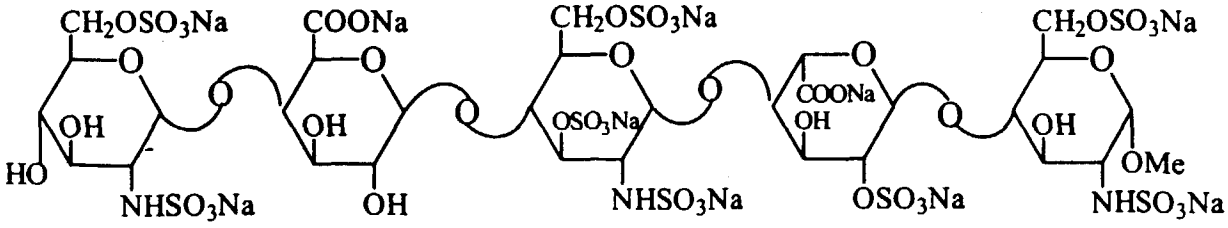
DRUG PRODUCT NAME

Tripolis 300
Burgerweeshispad 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:

α-D-glucopyranoside, methyl O-2-deoxy-6-O-sulfo-2-(sulfoamino)-α-D-glucopyranosyl-(1→4)-O-β-D-glucopyranuronosyl-(1→4)-O-2-deoxy-3,6-di-O-sulfo-2-(sulfoamino)-α-D-glucopyranosyl-(1→4)-O-2-O-sulfo-α-L-idopyranuronosyl-(1→4)-2-deoxy-2-(sulfoamino)-, 6-(hydrogen sulfate), decasodium salt.



Molecular Weight: 1728
Molecular Formula: C_{31} H_{43} N_3 Na_{10} O_{49} S_8

Consults:	**Status**
- Biopharmaceutics	pending
- Microbiology	Adequate
- CDRH (Delivery Device)	Adequate
- Office of Post-Marketing Drug Risk Assessment (4/20/01). The office did not recommend the use of 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.	Completed

- 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)

APPEARS THIS WAY
ON ORIGINAL

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 [redacted] are deficient

Ali Al-Hakim, Review Chemist

APPEARS THIS WAY
ON ORIGINAL

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/

Ali Al-Hakim
8/6/01 01:15:38 PM
CHEMIST

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

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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
ORIGINAL	Feb-15-2001	Feb-15-2001	Feb-15-2001
AMENDMENT	Jan-22- 2001	Jan-24-2001	Jan-24-2001
AMENDMENT	Mar-21-2001	Mar-22-2001	Mar-22-2001
AMENDMENT	Jun-20-2001	June-21-2001	Jun-22-2001

NAME & ADDRESS OF APPLICANT: Fonda BV

DRUG PRODUCT NAME

Tripolis 300
Burgerweeshispad 311
1076 HS Amsterdam, The Netherlands

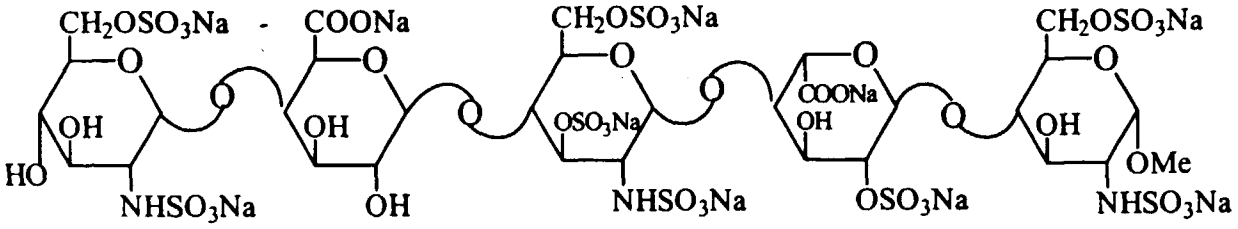
Proprietary:	Arixtra ™®
Established:	Fondaparinux
Code Name /#:	Org31540/SR90107A
Chem.Type/Ther.Class:	1/P

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:

α-D-glucopyranoside, methyl O-2-deoxy-6-O-sulfo-2-(sulfoamino)-α-D-glucopyranosyl-(1→4)-O-β-D-glucopyranuronosyl-(1→4)-O-2-deoxy-3,6-di-O-sulfo-2-(sulfoamino)-α-D-glucopyranosyl-(1→4)-O-2-O-sulfo-α-L-idopyranuronosyl-(1→4)-2-deoxy-2-(sulfoamino)-, 6-(hydrogen sulfate), decasodium salt.



Molecular Weight: 1728
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III			Adequate	R.Harapanhalli HFD-160 08/17/00	12/04/2000
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III			Adequate Information is provided in the NDA	Veterinary Med. 08/03/2000 Information is satisfactory	12/05/2000 12/05/2000

RELATED DOCUMENTS (if applicable): IND

Consults:

		Date Submitted	Status
-	Biometrics	February 15, 2001	pending
-	Biopharmaceutics	February 15, 2001	pending
-	Microbiology	February 15, 2001	pending
-	CDRH (Delivery Device)	February 15, 2001	Pending
-	Office of Post-Marketing Drug Risk Assessment (OPDRA) The office does not recommend the use of use of the propriety name "Xantidar". However, OPDRA has no objection to the use of the name "Arixtra". See OPDRA report dated April 20, 2001.	February 15, 2001	Completed (4/20/01)
-	Establishment Evaluation Report	March 05, 2001	pending.

Remarks:
The drug substance is manufactured used 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

APPEARS THIS WAY
ON ORIGINAL

Linag Zhou, Chemistry Team Leader

cc:
Org. NDA 21-345
HFD-180/Division File
HFD-180/A.Al-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