

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-484

CHEMISTRY REVIEW(S)

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
(HFD-180)

Review of Chemistry, Manufacturing, and Controls

JUL 6 2000

NDA #: 20-484

CHEM.REVIEW #: 2

REVIEW DATE: 07/03/2000

SUBMISSION TYPE

Amendment (BZ)

DOCUMENT DATE

05/15/2000

CDER DATE

05/16/2000

ASSIGNED DATE

05/19/2000

NAME & ADDRESS OF APPLICANT:

DuPont Pharmaceutical Company
Chestnut Run Plaza
Centre Road
Wilmington, DE 19805

DRUG PRODUCT NAME

Proprietary: Innohep®
Nonproprietary/USAN: Tinzaparin Sodium Injection
Code Name/#: N/A
Chem.Type/Ther.Class: I/S
ANDA Suitability Petition/DESI/Patent Status: Not Applicable

PHARMACOL.CATEGORY/INDICATION:

Treatment of acute deep vein thrombosis (DVT), with and without pulmonary embolism (PE) when administered in conjunction with warfarin sodium;

DOSAGE FORM:

Injection (solution)

STRENGTHS:

10,000 Iu/ml and 20,000 Iu/ml

ROUTE OF ADMINISTRATION: Subcutaneous

DISPENSED:

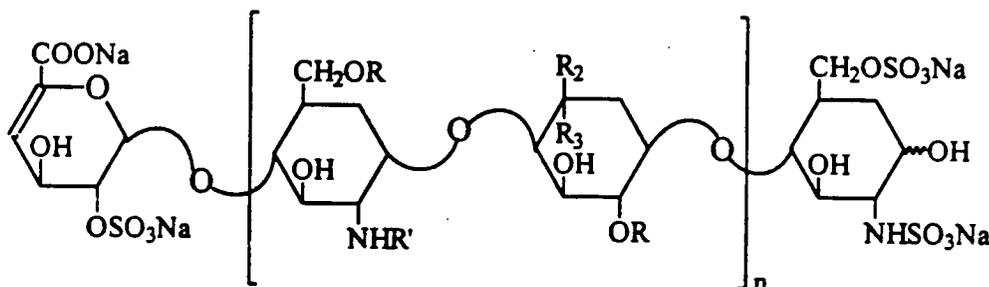
Rx OTC

Special Product

Yes No

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:

The majority of the chains have a 2-O-sulpho-4-enepranosulfonic acid structure at the non-reducing end and a 2-N,6-O-disulpho-D-glucosamine structure at the reducing end of the chains.



n=1 to 25, R=H or SO₃Na R'=H or SO₃Na or COCH₃
R₂=H and R₃=COONa or R₂=COONa and R₃=H
Weight Average Molecular Weight: 5500-7500 Dalton

SUPPORTING DOCUMENTS:

The following is the list of the Drug Master Files related to the application.

DMF / Type	Subject/Item Reviewed	Holder	Status	Review Date and Reviewer Name	Letter Date
			Adequate	06/09/2000 Ali Al-Hakim, HFD-180	
			Adequate	06/15/2000 Ali Al-Hakim HFD-180	
			Acceptable	1/12/1998 Paul Dietze HFD-150	
			Acceptable	2/18/1998 Joseph Sieczkowski HFD-180	
			Acceptable	06/29/1999 Ali Al-Hakim, HFD-180	

RELATED DOCUMENTS (if applicable): None

CONSULTS:

Biopharmaceutics

Pending

Trade Name

Acceptable

Biostatistics

Pending

Microbiology

The microbiology section of the NDA was consulted to the microbiology reviewer Dr. Paul Stivanage, HFD-805. Dr. Stivanage concluded, in his review, that the microbiology section of the NDA is satisfactory (review dated September 03, 1999).

REMARKS/COMMENTS:

- This review will evaluate the responses received from the applicant regarding our CMC information request letter dated April 28, 2000.
- Office of Product Drug Risk Assessment OPDRA found the name "Innohep" unacceptable. See OPDRA review dated stamped May 12, 2000. The applicant was notified to submit a new trade name.

APPEARS THIS WAY
ON ORIGINAL

CONCLUSIONS & RECOMMENDATIONS:

The NDA holder provided satisfactory responses to our information requests letter dated April 28, 2000. Based on satisfactory real time stability data provided (24 months), we recommend a tentative expiration period of 30 months for the drug product stored at 25°C.

The NDA may now be approved from the Chemistry, Manufacturing and Control point of view.

ISI 07/03/00
Ali Al-Hakim, Ph.D.
Review Chemist, HFD-180

ISI 7/6/00
Liang Zhou, Ph.D.
Chemistry Team Leader, HFD-180

cc:
Orig. NDA 20-484
HFD-180/Division File
HFD-180/L.Talarico
HFD-180/AAI-Hakim
HFD-180/CSO/K.Oliver
HFD-820/J.Gibbs
R/D Init by: L.Zhou

**DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
(HFD-180)**

Review of Chemistry, Manufacturing, and Controls

NDA #: 20-484

CHEM.REVIEW #: 1

REVIEW DATE: 02/22/2000

SUBMISSION TYPE

Original

DOCUMENT DATE

06/30/1999

CDER DATE

07/01/1999

ASSIGNED DATE

07/06/1999

NAME & ADDRESS OF APPLICANT:

DuPont Pharmaceutical Company
Chestnut Run Plaza
Centre Road
Wilmington, DE 19805

DRUG PRODUCT NAME

Proprietary: Innohep®
Nonproprietary/USAN: Tinzaparin Sodium Injection
Code Name/#: N/A
Chem. Type/Ther. Class: I/S
ANDA Suitability Petition/DESI/Patent Status: Not Applicable

PHARMACOL.CATEGORY/INDICATION:

Treatment of acute deep vein thrombosis (DVT), with and without pulmonary embolism (PE) when administered in conjunction with warfarin sodium;

DOSAGE FORM:

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STRENGTHS:

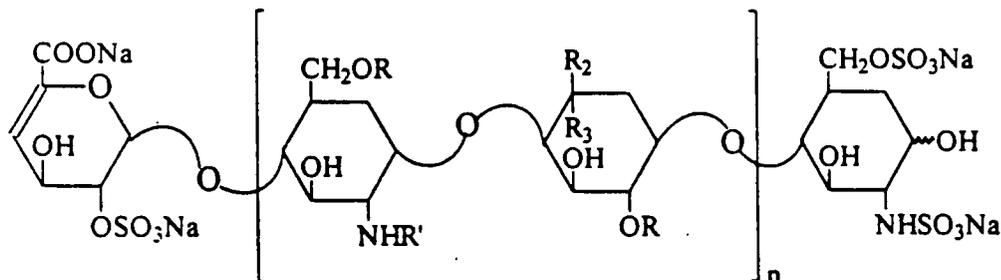
10,000 Iu/ml and 20,000 Iu/ml

ROUTE OF ADMINISTRATION:

Subcutaneous

DISPENSED: Rx OTCCHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,MOL.WT:

The majority of the chains have a 2-O-sulpho-4-eneopyranosulfonic acid structure at the non-reducing end and a 2-N,6-O-disulpho-D-glucosamine structure at the reducing end of the chains.



$n=1$ to 25, $R=H$ or SO_3Na $R''=H$ or SO_3Na or $COCH_3$
 $R_2=H$ and $R_3=COONa$ or $R_2=COONa$ and $R_3=H$
 Weight Average Molecular Weight: 5500-7500 Dalton

SUPPORTING DOCUMENTS:

The following is the list of the Drug Master Files related to the application.

DMF / Type	Subject/Item Reviewed	Holder	Status	Review Date and Reviewer Name	Letter Date
			Inadequate	12/27/1999 Ali Al-Hakim, HFD-180	To be sent
			Inadequate	02/10/2000	To be sent
			Acceptable	1/12/1998 Paul Dietze HFD-150	
			Acceptable	2/18/1998 Joseph Sieczkowski HFD-180	

RELATED DOCUMENTS (if applicable): None

CONSULTS:

Biopharmaceutics

Pending

Biostatistics

Pending

Microbiology

The microbiology section of the NDA was consulted to the microbiology reviewer Dr. Paul Stivanage, HFD-805. Dr. Stivanage concluded, in his review, that the microbiology section of the NDA is satisfactory (review dated September 03, 1999).

REMARKS/COMMENTS:

The proposed propriety name, innohep, was reviewed by the office of Post-marketing Drug Risk Assessment. The office concluded that the proposed name is unacceptable and that the firm should be requested to submit a new name for review and subsequent evaluation.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

CONCLUSIONS & RECOMMENDATIONS:

This NDA is approvable from Chemistry, Manufacturing and Control point of view; however, the NDA applicant has to provide additional information delineated in the draft deficiency letter at the end of this review.

1S/ 02/22/00

Ali Al-Hakim, Ph.D.
Review Chemist, HFD-180

1S/ 2/22/00

Liáng Zhóu, Ph.D.
Chemistry Team Leader, HFD-180

cc:
Orig. NDA 20-484
HFD-180/Division File
HFD-180/L.Talarico
HFD-180/AAI-Hakim
HFD-180/CSO/K.Oliver
R/D Init by: L.Zhou
