CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-715

Chemistry Review(s)

Printed by John Gibbs

Electronic Mail Message

Date: 13-Jun-2000 02:03pm
From: John Gibbs
GIBBS
Dept: HFD-820 PKLN 14B31
Tel No: 301-827-6420 FAX 301-827-0878

O: Bronwyn Collier (COLLIERB)
O: Jeanine Best (BESTJ)

C: Moo-Jhong Rhee (RHEEM)
C: David Lin (LINDAV)
ubject: Tertiary Chemistry Review of NDA 20-715

DA #20-715

rug: TRELSTAR (triptorelin pamoate for injection)

DA #20-715

rug: Trelstar (triptorelin pamoate for injection)

of Letter: APPROVAL

(

iemistry Tertiary Review #1

\: EIAR submitted with original application. FONSI signed Feb. 26, 1997.

icrobiology: Microbiologists Review #3 dated May 4, 2000 (secondary review / P. Cooney Ph.D. dated 5/5/2000) recommends the NDA for APPROVAL.

:adename: OPDRA consult #00-0041 dated 5/18/00 states there are no >jections to the proprietary name Trelstar.

ibeling: Revised labeling is being forwarded with the action letter.

:R: Satisfactory per EES dated Feb. 6, 2000.

:thods Validation: Pending. See memo to NDA 20-715 dated June 12, 2000.

IC: Per Chemistry Review #3 dated 22 May 200 and memo dated June 12, 2000 :ited above) NDA #20-715 is recommended for APPROVAL from the area of iemistry, Manufacturing, and Controls.

/S/

John J. Gibbs, Ph.D
Director, DNDC II

MAY 19 2000

Summary of Chemistry Review of NDA 20-715

A. Drug Substances:

Triptorelin pamoate is a new molecular entity analog of GnRH for palliative treatment of **advanced prostate cancer.** It is manufactured and supplied by [redacted] and the facility involved is deemed **in compliance to cGMP.**

The structure of peptide has been elucidated with [redacted] and all available data including [redacted] suggest that the proposed structure is correct.

The quality of triptorelin is adequately controlled by the following tests and specifications: description, identification [redacted] amino acid analysis, specific optical rotation, water content, pamoic acid content, peptide content, purity [redacted] related impurities [redacted] residual acetic acid.

Based on available data, the drug substance is stable for [redacted] years when stored at [redacted]

The established name, **triptorelin pamoate**, has not been approved by USAN. However, since **"triptorelin"** was approved previously and the sponsor committed to apply for approval of "triptorelin pamoate" to USAN (a copy of the application was submitted), the use of "triptorelin pamoate" as an established name for this drug is deemed acceptable per discussion with Dr. Dan Boring, Chair of the Labeling and Nomenclature Committee.

B. Drug Product:

This is a new GnRH agonist depo formulation presented as **microgranules** which are manufactured by **Debio Recherche Pharmaceutique S.A.**, Switzerland, sterilized at [redacted] and packaged at **The Upjohn Co.**, Michigan. Sterility testing were done at either [redacted] All facilities are **in compliance to cGMP.**

The lyophilized microgranules in a vial contain contain 3.75mg of triptorelin (free base) as well as dl-lactide-glycolide polymer (170mg), manitol (85mg), carboxymethylcellulose sodium (30mg), and polysorbate 80 (2mg).

The lyophilized microgranules are to be reconstituted with **sterile water for injection** before intramuscular injection. Originally, the product was co-packaged with a sterile water for injection, but later the sponsor proposed to delete the diluent and market the vial only. The sponsor has demonstrated that use of different readily available diluent such as saline (0.45% and 0.9%) and 5% dextrose in 0.45% sodium chloride did not significantly affect the in-vitro dissolution profile. However, since *in vitro/in vivo* correlation has not been established for this product, it was decided that *in vitro* test is not adequate to address the bioavailability of the product using different diluents. Therefore, **use of sterile water** was mandated in the labeling as well as labels.

The quality of the lyophilized microgranules is adequately controlled by tests such as appearance, identification [redacted] strength [redacted], content uniformity [redacted], related impurities [redacted] in-vitro dissolution, water content, particle size, content of pamoic acid [redacted] sterility, and pyrogenicity (rabbit).

The microgranules are packaged in a type I tubing glass vial with a [redacted] stopper with [redacted] overseal. The container/closure system is considered to be adequate for protecting the product during the shelf life.

Based on available stability data [redacted] expiry date is granted.

The tradename, **Trelstar**, was accepted by OPDRA, and the labeling as well as labels are deemed in compliance to the labeling requirements.

C. Conclusion and Recommendation:

As recommended by the primary reviewer, this NDA can be approved from chemistry point of view.

5/19/00

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader
For the Division of reproductive and Urologic Drug Products
DNDC II, Office of New Drug Chemistry

MAY 22 2000

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS - HFD-580

Review of Chemistry, Manufacturing and Controls

NDA #: 20-715
CHEMISTRY REVIEW #: 3 **DATE REVIEWED:** 22-MAY-2000

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	30-OCT-98	30-OCT-98	03-NOV-98
Amendment	19-MAY-00	22-MAY-00	

NAME & ADDRESS OF SPONSOR:
Debio Recherche Pharmaceutique
Case Postale
Route du Levant 146
CH-1920 Martigny, Switzerland
US Agent: Robert J. McCormack, Ph.D.
Target Research Associates
1801 East Second Street
Scotch Plains, NJ 07076

DRUG PRODUCT NAME:

Proprietary:	Trelstar
Nonproprietary/Established/USAN:	Triptorelin pamoate
Code Name/#:	D-Trp6-LHRH
Chem.Type/Ther.Class:	1S

PARMACOLOGICAL CATEGORY/INDICATION: LHRH agonist/Palliative treatment for advanced prostate cancer

DOSAGE FORM: Lyophilized powder to be reconstituted (water for injection) for Injection

STRENGTHS: 3.75 mg

ROUTE OF ADMINISTRATION: Intramuscular (IM) injection

DISPENSED: ___x___ Rx _____ OTC

SPECIAL PRODUCTS: ___ Yes _x_ No

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

5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-tryptophyl-L-leucyl-L-arginyl-L-prolylglycinamide (pamoate salt) [(pyro)Glu-His-Trp-Ser-Tyr-D-Trp-Leu-Arg-Pro-Gly-NH_2, pamoate salt]

see Chemistry Review #2 for structural formula

$C_{64}H_{82}N_{18}O_{13} \bullet C_{23}H_{16}O_6$ (pamoic acid)
MW 1699.9 (triptorelin 1311.5 + pamoic acid 388.4)

SUPPORTING DOCUMENTS:

See Chemistry Review #2.

RELATED DOCUMENTS:

none

PATENT STATUS:
See Chemistry Review #1.

CONSULTS:

The proposed trademark, Trelstar, was reviewed by OPDRA and determined to be acceptable.

REMARKS/COMMENTS:

The May 22, 2000 amendment contains the sponsor's commitment to pursue USAN approval of the name triptorelin pamoate, along with a copy of the USAN application. This amendment also contains revised labeling and revised container/cartons labels. The container label was missing the established name and this omission was conveyed to the sponsor. The sponsor stated that this was an oversight and was corrected in the amendment.

The May 2, 2000 T-con with the sponsor related to the issue of the batch formula that was raised in Comment #6 of the CMC section in the June 26, 1997 FDA non-approvable letter. The information provided during the T-con did not add to the information that was previously provided in the February 11, 1999 amendment.

CONCLUSIONS & RECOMMENDATIONS:
This NDA may be approved from a CMC point of view.

cc:
Orig. NDA #20-715
HFD-580/Division File
HFD-580/JBest
HFD-580/MRhee/DLin
HFD-820/JGibbs/SKoepke

S 5/22/00
David T. Lin, Ph.D.
Review Chemist

R/D Init by:

filename: nda20715.3 (doc) S 5/22/00

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MAY 18 2000

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS - HFD-580

Review of Chemistry, Manufacturing and Controls

NDA #: 20-715

CHEMISTRY REVIEW #: 2 **DATE REVIEWED:** 18-MAY-2000

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	30-OCT-98	30-OCT-98	03-NOV-98
Amendment	11-FEB-99	12-FEB-99	
Amendment	16-DEC-99	16-DEC-99	
Amendment	11-MAY-00	12-MAY-00	
Amendment	12-MAY-00	15-MAY-00	
Amendment	15-MAY-00	16-MAY-00	

NAME & ADDRESS OF SPONSOR:

Debio Recherche Pharmaceutique
Case Postale
Route du Levant 146
CH-1920 Martigny, Switzerland
US Agent: Robert J. McCormack, Ph.D.
Target Research Associates
1801 East Second Street
Scotch Plains, NJ 07076

DRUG PRODUCT NAME:

Proprietary:	Trelstar
Nonproprietary/Established/USAN:	Triptorelin pamoate
Code Name/#:	D-Trp6-LHRH
Chem.Type/Ther.Class:	1S

PARMACOLOGICAL CATEGORY/INDICATION: LHRH agonist/Palliative treatment for advanced prostate cancer

DOSAGE FORM: Lyophilized powder to be reconstituted (water for injection) for Injection

STRENGTHS: 3.75 mg

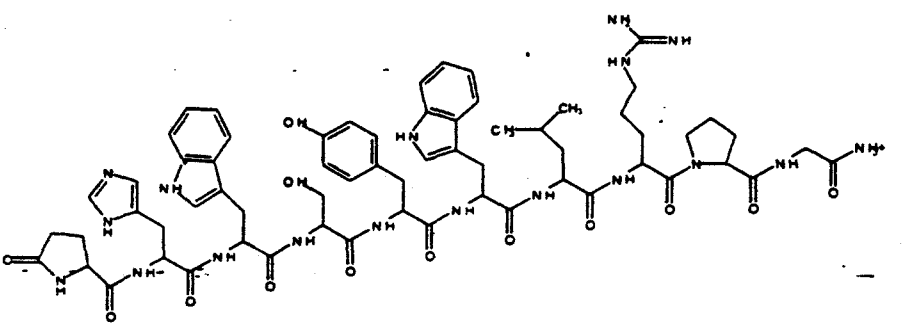
ROUTE OF ADMINISTRATION: Intramuscular (IM) injection

DISPENSED: __x__ Rx _____ OTC

SPECIAL PRODUCTS: __ Yes __x__ No

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

5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-tryptophyl-L-leucyl-L-arginyl-L-prolylglycinamide (pamoate salt) [(pyro)Glu-His-Trp-Ser-Tyr-D-Trp-Leu-Arg-Pro-Gly-NH_2, pamoate salt]



$C_{64}H_{82}N_{18}O_{13} \bullet C_{23}H_{16}O_6$ (pamoic acid)
MW 1699.9 (triptorelin 1311.5 + pamoic acid 388.4)

SUPPORTING DOCUMENTS:

Type/Number	Subject	Holder	Status	Review Date	Letter Date
DMF	Triptorelin pamoate		Adequate	5/15/00	N/A
DMF			Adequate	5/16/97	N/A
DMF			N/A	N/A	N/A
DMF			Adequate	3/14/00	N/A
DMF			Adequate	9/15/99	N/A
DMF			Adequate	5/5/00	N/A

RELATED DOCUMENTS:
none

PATENT STATUS:
See Chemistry Review #1.

CONSULTS:

1. The Division of Biopharmaceutics has been consulted for the dissolution specifications. The reviewer's proposed specifications have been agreed upon with the sponsor (5/11/00 amendment).
2. An EER was submitted on January 20, 2000 and an overall acceptable recommendation from the Office of Compliance was issued on February 2, 2000 (see Appendix A).
3. The proposed trademark, Trelstar, is pending OPDRA review.
4. The Microbiology Staff was consulted to review the Microbiology section. After review (see Micro Review #3 dated 5/5/00), they have recommended approval.

REMARKS/COMMENTS:
See Chemistry Review #1 for a description of the drug substance peptide and drug product.

The February 11, 1999 amendment contains the response to the CMC deficiencies outlined in the FDA non-approvable letter dated June 26, 1997.

The December 16, 1999 amendment contains the rationale for withdrawal of the Debioject and Debioclip delivery systems and replacement of the vial alone package configuration, and other CMC information.

The May 11, 2000 amendment contains a statement of agreement to the FDA proposed dissolution specifications.

The May 12, 2000 amendment contains a statement of agreement that the to-be-marketed product will be manufactured with only the [redacted]

The May 15, 2000 amendment contains mock-ups of the carton and vial labels.

CONCLUSIONS & RECOMMENDATIONS:

This NDA may be approved from a CMC point of view pending satisfactory resolution of the Trademark review and final carton label comments.

cc:
Orig. NDA #20-715
HFD-580/Division File
HFD-580/JBest
HFD-580/MRhee/DLin
HFD-820/JGibbs/SKoepke

/S/ 5/16/00
David T. Lin, Ph.D.
Review Chemist

R/D Init by: /S/ 5/18/00

filename: nda20715.2 (doc)

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Memorandum

To: NDA 20-715, Decapeptyl (triptorelin - noate for depot suspension) 3.75 mg

Through: Moo-Jhong Rhee, Ph.D. /S/ 8/12/99

From: David Lin, Ph.D. 8/12/99

Date: August 11, 1999 /S/

Re: Request for packaging change dated June 18, 1999.

NDA 20-715 was issued a non-approvable (NA) letter on June 26, 1997, which included a list of deficiencies. The sponsor responded to the biopharmaceutics, chemistry and manufacturing controls, and microbiological issues on February 11, 1999, as a partial response to the NA letter. In a correspondence dated June 18, 1999, the sponsor has requested to change the packaging configuration from the Debioject single dose delivery system to the Decapeptyl vial alone. The Debioject delivery system includes the [redacted] sterilized vial connected to the — sterilized Debioject syringe unit. The sponsor states that consideration of the vial alone package would not involve the review of any additional data. However, the following discussion demonstrates that there will be additional data that would require review.

Since the pre-filled syringe would not be part of the packaged product, there are concerns resulting from the potential multiple use of a large size container of sterile water, the potential for use of the incorrect volume of sterile water, and the potential use of other diluents, such as saline or half-strength saline. There are no data to show the effect of other diluents on the resuspendablity of the lyophilized product. In addition, the effect of using different size syringes and needles has not been determined. Comparability studies with all potential candidate diluents, syringes and needles will have to be performed to demonstrate that delivery, as well as sterility, of the drug product is not affected. **Based on having to review a substantial amount of new data that are not limited to the deficiencies in the non-approval letter, this request for a packaging change is not acceptable.**

The one part of the NDA that would not require additional review concerns the stability data. Since the Debioject delivery system includes the drug product vial, additional stability data on just the drug product vials would not be needed.

cc:
Orig. NDA #20-715
HFD-580/Division File
HFD-580/KColangelo
HFD-580/MRhee/DLin

Filename: nda20715packchange.doc

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS, HFD-580
Review of Chemistry, Manufacturing and Controls

MAY 16 1997

NDA #: 20-715
CHEMISTRY REVIEW #: 1
DATE REVIEWED: 5-16-97

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	6-24-96	6-26-96	7-8-96
AMENDMENT	9-19-96	9-19-96	
	1-27-97	1-31-97	
	3-26-97	3-28-97	
	5-2-97	5-5-97	

ORIGINAL

NAME & ADDRESS OF APPLICANT:
Debio Recherche Pharmaceutique SA
Case Postale, Route du Levant 146
CH-1920 Martigny, Switzerland
US Agent: N. Peter Kostopulos
Kostopulos & Associates
205 S. Whiting Street
Suite 201, Alexandria, VA 22304

DRUG PRODUCT NAME

Proprietary:	Decapeptyl Depot
Nonproprietary/Established/USAN:	Triptorelin
Code Name/#:	D-Trp^6-LHRH
Chem.Type/Ther.Class:	1S

ANDA Suitability Petition / DESI / Patent Status: N/A [if applicable]

PHARMACOLOGICAL CATEGORY/INDICATION: LHRH agonist/Palliative Treatment of Advanced Carcinoma of the Prostate

DOSAGE FORM: Lyophilized Powder to be reconstituted (water for injection) for Injection

STRENGTHS: 3.75mg/vial

ROUTE OF ADMINISTRATION: Intramuscular Injection (IM)

DISPENSED: _X_ Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
(pyro)Glu-His-Trp-Ser-Tyr-D-Trp-Leu-Arg-Pro-Gly-NH_2

C64H82N18O13
MW = 1311.48

CONCLUSIONS & RECOMMENDATIONS:
This NDA is not approvable from chemistry point of view. See draft letter.

cc:
Org. NDA
HFD-580/Division File
HFD-580/MRhee/ADunson
HFD-820/JGibbs (NME only)
R/D Init by:
filename: N20715#1

/S/
Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader

SUPPORTING DOCUMENTS:

DMF
DMF
DMF
DMF

RELATED DOCUMENT: IND IND

CONSULTS:

Micobiology: Rev #1 Sep-9-97 was done with deficiencies.
EA: FONSI was signed off on Feb-26-97
EER was forwarded on Aug-6-97

REMARKS/COMMENTS:

This NDA describes a new LH-RH agonist analog for palliative treatment of advanced prostate cancer. This analog contains D-triptophane at 6th position of the natural LH-RH. The formuation is very similar to Lupron Depot products previously approved, except that this product is microgranules as opposed to microspheres. Originally, the product was proposed as microspheres containing triptorelin acetate, however, during the course of the development, it was changed to microgranules containing triptorelin pamoate. This was due to deletion of from the manufacturing process of microspheres rwsulting in switching to microgranules. Microgranules have higher release rate compared to microspheres and therefore triptorelin pamoate was substituted for the acetate form to counter the higher release rate with lower solubility of pamoate form. Most clinical studies were done with acetate form and this has been subject of the biequivalence issue.

Amendment dated Sep-19-96 was submitted in response to question on the batch records.
Amendment dated Jan-27-97 was submitted in response to deficiencies of Environmental Assessment.
Amendment dated Mar-26-97 was submitted for the modified in-vitro dissolution testing.
Amendment dated May-2-97 was submitted for the new trade name

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DMF: [redacted] DMF Type: II
Title: Decapeptyl (triptorelin pamoate)

1. CHEM REVIEW # 4 2. REVIEW DATE: 10-MAY-2000

3. ITEM REVIEWED
A. IDENTIFICATION
USAN: Tritorelin pamoate
Ingredient Dictionary name: Triptorelin pamoate
Manufacturer's code: None
Chemical name: 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-tryptophyl-L-leucyl-L-arginyl-L-prolylglycinamide (pamoate salt)
CAS number: 57773-63-4

H-5-oxoPro-His-Trp-Ser-Tyr-D-Trp-Leu-Arg-Pro-Gly-NH_2

B. LOCATION IN DMF

Type of Submission	Date of Submission	Location of Information
Response to FDA letter	21-FEB-2000	Vol. 1.1

4. PREVIOUS DOCUMENTS:

Type of Document	Date of Document	Comment
Original submission	28-Apr-1986	Chem. Rev. #1 by Dr. J. Blumenstein
Amendment	17-Aug-1988	Chem. Rev. #1 by Dr. J. Blumenstein
Review #1	09-Oct-1990	Deficient
Deficiency letter	12-Nov-1990	
Resubmission	16-Apr-1996	Chem. Rev. #2 by Dr. M.J. Rhee
Review #2	16-May-1997	Deficient
Deficiency letter	12-Jun-1997	
Resubmission	10-Jul-1997	Chem. Rev. #3 by Dr. D.T. Lin
Review #3	20-Jul-1999	Deficient
Deficiency letter	21-Oct-1999	

5. NAME AND ADDRESS OF DMF HOLDER AND REPRESENTATIVE(S):
Name:
Address:

Representative:

Representative or U.S. Agent:
Name:
Address:

Contact Person's Name:

Address:
Telephone:

6. DMF REFERENCED FOR:

NDA:	20-715	
APPLICANT:	Debio Recherche Pharmaceutique S.A.	
LOA:	5/15/98	
DRUG PRODUCT NAME:	Trelstar	
DOSAGE FORM:	Lyopholized powder for suspension	CODE: 834
STRENGTH:	3.75 mg	
ROUTE OF ADMINISTRATION:	Intramuscular injection	CODE: 005

7. SUPPORTING DOCUMENTS: None

8. CURRENT STATUS OF DMF:
DATE OF LAST UPDATE OF DMF: February 21, 2000
DATE OF MOST RECENT LIST OF COMPANIES FOR WHICH LOA's HAVE BEEN PROVIDED: none

9. CONSULTS: None

10. COMMENTS:
Reviewed drug substance peptide, triptorelin pamoate. This DMF is reviewed in support of NDA 20-715.

11. CONCLUSION:
This DMF is adequate to support the NDA.

/S/ 5/10/00
David T. Lin, Ph.D.
Review Chemist, HFD-580

cc:
Orig. DMF # [redacted] (2 copies)
HFD-580/Div. File NDA 20-715
HFD-580/CSO/JBest
HFD-580/Chemist/MJRhee/DTLin
R/D Init

Filename [redacted] (doc)

/S/ 5/12/00
Moo-Jhong Rhee, Ph.D.
Team Leader, HFD-580

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MAY 19 2000

Memorandum

To: NDA 20-715, Trelstar (triptorelin pamoate for injection), 3.75 mg

Through: Moo-Jhong Rhee, Ph.D.

From: David Lin, Ph.D. 5/19/00

Date: May 19, 2000

Re: Chemistry Review #3 for DMF #[redacted]

Chemistry Review #3 for DMF [redacted] is [redacted] However, since NDA 20-715 is for the same drug product, but for a different indication, Chemistry Review #3 is relevant to this NDA. Therefore, the issues identified in that review were addressed in Chemistry Review #4.

cc:
Orig. NDA #20-715
HFD-580/Division File
HFD-580/JBest
HFD-580/MRhee/DLin

Filename: nda20715dmf.doc

DMF: [redacted] DMF Type: II

JUL 16 1999

Title: Decapeptyl (triptorelin pamoate)

1. **CHEM REVIEW #** 3

2. **REVIEW DATE:** 16-JUL-1999

3. **ITEM REVIEWED**

A. IDENTIFICATION

USAN: Tritorelin pamoate

Ingredient Dictionary name: Triptorelin pamoate

Manufacturer's code: None

Chemical name: 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-tryptophyl-L-leucyl-L-arginyl-L-prolylglycinamide (pamoate salt)

CAS number: 57773-63-4

H-5-oxoPro-His-Trp-Ser-Tyr-D-Trp-Leu-Arg-Pro-Gly-NH_2

B. LOCATION IN DMF

Type of Submission	Date of Submission	Location of Information
Response to FDA letter	10-Jul-1997	Vol. 1.1

4. **PREVIOUS DOCUMENTS:**

Type of Document	Date of Document	Comment
Original submission	28-Apr-1986	Chem. Rev. #1 by Dr. J. Blumenstein
Amendment	17-Aug-1988	Chem. Rev. #1 by Dr. J. Blumenstein
Review #1	09-Oct-1990	Deficient
Deficiency letter	12-Nov-1990	
Resubmission	16-Apr-1996	Chem. Rev. #2 by Dr. M.J. Rhee
Review #2	16-May-1997	Deficient
Deficiency letter	12-Jun-1997	

5. **NAME AND ADDRESS OF DMF HOLDER AND REPRESENTATIVE(S):**

Name:
Address:

[redacted]

Representative:

Representative or U.S. Agent:
Name:
Address:

Contact Person's Name: [redacted]

Address:
Telephone:

6. **DMF REFERENCED FOR:**

NDA: [redacted]
APPLICANT: Debio Recherche Pharmaceutique S.A.
LOA:
DRUG PRODUCT NAME:
DOSAGE FORM: CODE:
STRENGTH:
ROUTE OF ADMINISTRATION: CODE:

7. **SUPPORTING DOCUMENTS:** None

8. **CURRENT STATUS OF DMF:**

DATE OF LAST UPDATE OF DMF: July 10, 1997
DATE OF MOST RECENT LIST OF COMPANIES FOR WHICH LOA's HAVE BEEN PROVIDED: none

9. **CONSULTS:** None

10. **COMMENTS:**

Reviewed drug substance peptide, triptorelin pamoate. This DMF is reviewed in support of [redacted]

11. **CONCLUSION:**

This DMF will be adequate to support the NDA pending satisfactory resolution of the deficiencies delineated in the draft letter.

/S/ 7/16/99
David T. Lin, Ph.D.
Review Chemist, HFD-580

cc:
Orig. DMF # [redacted] 2 copies)
HFD-580/Div. File NDA 21-002 (Chem. Rev. #1)
HFD-580/CSO/EDeGuia
HFD-580/Chemist/MJRhee/DTLin
R/D Init

Filename: [redacted] doc)

/S/ 7/16/99
Moo-Jhong Rhee, Ph.D.
Team Leader, HFD-580

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MAY 0 3 2000

DMF: [redacted] DMF Type: III
Title: Rubber Closure [redacted]

1. **CHEM REVIEW # 1** 2. **REVIEW DATE:** 03-MAY-2000

3. **ITEM REVIEWED**
   A. IDENTIFICATION
   Tradename: Rubber closure [redacted]
   USAN:
   Ingredient Dictionary name:
   Manufacturer's code:
   Chemical name:
   CAS number:

   B. LOCATION IN DMF

Type of Submission	Date of Submission	Location of Information
Amendment	18-May-1993	Vol. 22.1

4. **PREVIOUS DOCUMENTS:**

Type of Document	Date of Document	Comment
various		

5. **NAME AND ADDRESS OF DMF HOLDER AND REPRESENTATIVE(S):**
Name:
Address:

Representative:

Representative or U.S. Agent:
Name:
Address:

Contact Person's Name: same
Address: same
Telephone: [redacted]

6. **DMF REFERENCED FOR:**

NDA:	20-715	
APPLICANT:	Debio Recherche Pharmaceutique S.A.	
LOA:	6/18/98	
DRUG PRODUCT NAME:	Trelstar	
DOSAGE FORM:	Lyopholized powder for suspension	CODE: 834
STRENGTH:	3.75 mg	
ROUTE OF ADMINISTRATION:	Intramuscular injection	CODE: 005

7. **SUPPORTING DOCUMENTS:** None

8. CURRENT STATUS OF DMF:
DATE OF LAST UPDATE OF DMF: March 10, 2000
DATE OF MOST RECENT LIST OF COMPANIES FOR WHICH LOA's HAVE BEEN PROVIDED: none

9. CONSULTS: None

10. COMMENTS:
Reviewed rubber [redacted] This DMF is reviewed in support of NDA 20-715.

11. CONCLUSION:
This DMF is adequate to support the NDA.

/S/ 5/3/00

David T. Lin, Ph.D.
Review Chemist, HFD-580

cc:
Orig. DMF # [redacted] (2 copies)
HFD-580/Div. File NDA 20-715
HFD-580/CSO/JBest
HFD-580/Chemist/MJRhee/DTLin
R/D Init

/S/ 5/3/00

Moo-Jhong Rhee, Ph.D.
Team Leader, HFD-580

Filename: [redacted] (doc)

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DMF: [redacted] DMF Type: II
Title: Decapeptyl

1. CHEM REVIEW #: 2 2. REVIEW DATE: May 16, 1997 MAY 16 1997

3. DMF INFORMATION REVIEWED:

Type of Submission	Date of Submission	Location of Info.
Resubmission	April 16, 1996	Volume 1.1

4. PREVIOUS DOCUMENTS

Type of Document	Date of Document	Comment
Review #1	Oct-9-1990	Deficient
Deficiency Letter	Nov-12-1990	

5. NAME & ADDRESS OF DMF HOLDER AND REPRESENTATIVE(S):

Name:
Address: [redacted]

6. ITEM REVIEWED:

Decapeptyl (triptorelin pamoate)

7. DMF REFERENCED FOR:

NDA: 20-715
APPLICANT NAME: Debio Recherche Pharmaceutique SA, CH-1920 Martigny, Switzerland
LOA DATE: April 16, 1996
DRUG PRODUCT NAME: Not determined yet
DOSAGE FORM: Depot Suspension for Injection
STRENGTH: 3.75mg
ROUTE OF ADMINISTRATION: IM (monthly)

8. SUPPORTING DOCUMENTS: NA

9. CURRENT STATUS OF DMF:

DATE OF LAST UPDATE OF DMF: April 16, 1996
DATE OF MOST RECENT LIST OF COMPANIES FOR WHICH LOA's HAVE BEEN PROVIDED: April 16, 1996 for Debio Recherche Pharmaceutique S.A.

10. CONSULTS: None

11. REMARKS/COMMENTS: The original submission was reviewed by Dr. Jeffrey J. Blumenstein (HFD-150) on Oct-10-1990 and a deficiency letter was issued on Nov-2-1990. On Apr-16-1996, a new updated version was submitted which will supercede the previous submission and is the subject of this review.

12. CONCLUSIONS & RECOMMENDATIONS:

This DMF is considerd to be acceptable for supporting the NDA 20-715 pending satisfactory resolution of the deficiencies delineated in the draft letter.

/S/

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader, DNDC II, HFD-820
@Division of Reproductive and Urologic Drug Products, HFD-580

cc: DMF [redacted] (2 copies)
HFD-580/Division File NDA 20-715
HFD-580/MRhee/ADunson
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ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

Decapeptyl®

(triptorelin pamoate for injection)

Sterile Powder

NDA 20-715

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS

(HFD-580)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-715

Decapeptyl® Sterile Powder

(triptorelin pamoate for injection)

The National Environmental Policy Act of 1969 (NEPA) requires all Federal agencies to assess the environmental impact of their actions. FDA is required under NEPA to consider the environmental impact of approving certain drug product applications as an integral part of its regulatory process.

The Food and Drug Administration, Center for Drug Evaluation and Research has carefully considered the potential environmental impact of this action and has concluded that this action will not have a significant effect on the quality of the human environment and that an environmental impact statement therefore will not be prepared.

In support of their new drug application for **Decapeptyl® (triptorelin pamoate for injection) Sterile Powder, Debio Recherche Pharmaceutique S.A.** has prepared an environmental assessment in accordance with 21 CFR 25.31a (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Decapeptyl Sterile Powder will be administered by injection as a palliative treatment for patients with advanced prostate cancer. The drug substance will be manufactured by Switzerland and the drug product will be manufactured by Debio Recherche Pharmaceutique S.A., Martigny Switzerland. The finished drug product will be used in hospitals and clinics throughout the United States.

Triptorelin pamoate may enter the environment from excretion by patients, from disposal of pharmaceutical waste or from emissions from manufacturing sites. The projected environmental introduction concentration from use is less than 1 ppb. CDER has routinely found that concentrations less than 1 ppb have no effect on relevant standard test organism, therefore the applicant has submitted a Tier 0 EA without format items 7, 8, 9, 10 and 11.

Disposal in the United States may result from returned, recalled or expired goods and user disposal of empty or partly used product and packaging. Returned, recalled or expired goods will be sent to licensed disposal facility. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic procedures.

Precautions taken at the sites of manufacture of the bulk product and its final formulation are expected to minimize occupational exposures and environmental release.

The Center for Drug Evaluation and Research has concluded that the product can be manufactured, used and disposed of without any expected adverse environmental effects. Adverse effects are not anticipated upon endangered or threatened species or upon property listed in or eligible for listing in the National Register of Historic Places.

2/20/97 /S/

DATE PREPARED BY
Nancy B. Sager
Team Leader
Environmental Assessment Team
Center for Drug Evaluation and Research

2-27-97 /S/

DATE CONCURRED
Eric B. Sheinin, Ph.D.
Director, Office of New Drug Chemistry
Center for Drug Evaluation and Research

Attachment: Environmental Assessment

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NDA 20-715
Trelstar® Depot (triptorelin pamoate for injectable suspension)
Debio Recherche Pharmaceutique S.A.

The Establishment Inspection is satisfactory.

E L E C T R O N I C M A I L M E S S A G E

Sensitivity: COMPANY CONFIDENTIAL

Date: 12-Jun-1997 02:22pm EDT
From: Moo-Jhong Rhee
RHEEM
Dept: HFD-580 PKLN 17B45
Tel No: 301-443-3520 FAX 301-443-9282

TO: See Below

Subject: FWD: Decapeptyl, NDA 20-715

Ms. Ripper: I just heard from Bob Seevers, our EER focal point, that the inspection of foreign facilities involved in this NDA may not be done by DUFA goal date. This NDA has two separate EERs; one for manufacturing facilities and the other for contract laboratories. The latter was forwarded to OC later than the former because these contract laboratories were not listed in the "manufacturers" section of the NDA and they were found in other sections during the review.

If you have any question, please let me know.

Jhong

Distribution:

TO: Leah Ripper (RIPPER)

CC: Lana Pauls (PAULSL)
CC: Alvis Dunson (DUNSONA)
CC: Lisa Rarick (RARICK)
CC: John Gibbs (GIBBS)
CC: Robert Seevers (SEEVERSR)

E L E C T R O N I C M A I L M E S S A G E

ensitivity: COMPANY CONFIDENTIAL

Date: 12-Jun-1997 11:13am EDT
From: Alvis Dunson
DUNSONA
Dept: HFD-580 PKLN 17B45
Tel No: 301-827-4260 FAX 301-827-4267

): Leah Ripper (RIPPER)

: Lana Pauls (PAULSL)
: Moo-Jhong Rhee (RHEEM)
: Robert Seevers (SEEVERSR)

ıbject: Decapeptyl, NDA 20-715

ıah,

talked with the Division EER Coordinator, Bob Seevers, about this
ɔlication. According to EES, one inspection site in Switzerland has
assigned but not yet performed. Coordination has been made with
ɜsa Egas in the Office of Compliance to find out when the EER will
completed, but to date the EER remains pending. As soon as we have
answer we will let you know.

vis

for June 02, 1997

Application: **NDA 20715/000** Priority: **1S** Org Code: **580**

Stamp: **26-JUN-1996** Regulatory Due: **26-JUN-1997** Action Goal: District Goal: **24-FEB-1997**

Applicant: **DEBIO RECHERCHE**
RT DE LEVANT 146, CH-1920
MARTIGNY, , SZ

Brand Name: **DECAPEPTYL (TRIPTORELIN) DEPO**
Established Name:
Generic Name: **TRIPTORELIN**
Dosage Form: **INJ (INJECTION)**
Strength: **3.75 MG/VIAL**

FDA Contacts: **M. RHEE** **(HFD-580)** **301-827-4237 , Review Chemist**

Overall Recommendation:

Establishment: [redacted]

DMF No: [redacted]

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATIO 07-APR-1997**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities:

Establishment: [redacted]

DMF No:

Profile: **NEC** OAI Status: **NONE**
Last Milestone: **ASSIGNED INSPECTIO 06-MAR-1997**

Responsibilities:

Establishment: [redacted]

DMF No:

Profile: **NEC** OAI Status: **NONE**
Last Milestone: **INSPECTION PERFOR 02-JUN-1997**

Responsibilities:

Establishment: **9614420**
DEBIO RECHERCHE PHARMACEUT
ROUTE DU LEVANT 146, CH-1920
MARTIGY, , SZ

DMF No: [redacted]

Profile: **SVS** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATIO 29-APR-1997**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities:
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE STERILIZER

Establishment:	**1810189** **PHARMACIA AND UPJOHN CO** **7000 & 7171 PORTAGE RD** **KALAMAZOO, MI 49001**	DMF No:	
		Profile: **SVS**	OAI Status: **NONE**
		Last Milestone:	**OC RECOMMENDATIO 06-MAR-1997**
Responsibilities:		Decision:	**ACCEPTABLE**
FINISHED DOSAGE PACKAGER		Reason:	**BASED ON PROFILE**

Establishment:	[redacted]	DMF No:	
		Profile: **RSP**	OAI Status: **NONE**
		Last Milestone:	**OC RECOMMENDATIO 21-FEB-1997**
Responsibilities:	[redacted]	Decision:	**ACCEPTABLE**
		Reason:	**BASED ON PROFILE**

APPEARS THIS WAY ON ORIGINAL

Memorandum

To: NDA 20-715, Trelstar (triptorelin pamoate for injection), 3.75 mg

Through: Moo-Jhong Rhee, Ph.D. /S/ 6/12/00

From: David Lin, Ph.D. /S/ 6/12/00

Date: June 12, 2000

Re: Addendum to Chemistry Review #3

The Methods Validation section is currently pending, but it is not deficient. The sponsor has adequately addressed all the issues in the Methods Validation section. However, the corrected methods in the Methods Validation Package are now contained in various amendments to this NDA. Therefore, the sponsor will submit clean and updated copies of the Methods Validation Package, which will then be forwarded to the FDA laboratories for validation.

cc:
Orig. NDA #20-715
HFD-580/Division File
HFD-580/JBest
HFD-580/MRhee/DLin

Filename: nda20715adden.3doc

NDA 20-715
Trelstar® Depot (triptorelin pamoate for injectable suspension)
Debio Recherche Pharmaceutique S.A.

The Methods Validation is pending for this drug product.