CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-715

Microbiology Review(s)

Best

MAY - 5 2000

REVIEW FOR HFD-580
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW #3 OF NDA

May 4, 2000

A. 1. NDA 20-715/N-BZ

U.S. AGENT Target Research Associates
1801 East Second Street
Scotch Plains, NJ 07076

APPLICANT Debio Recherche Pharmaceutique SA
Route du Levant 146
CH-1920 Martigny
Switzerland

2. PRODUCT NAMES: Trelstar® Depot, 3.75 mg (triptorelin pamoate for injectable suspension)

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: The product is a lyophilized powder in a 6 cc vial with a rubber stopper. The depot powder consists of 3.75 mg of sterile triptorelin pamoate. The powder is reconstituted with 2 mL Sterile Water for Injection from a prefilled syringe. Microgranules of the active ingredient are suspended in the diluent, and are injected intramuscularly, once each month. The drug product is to be administered as a single monthly intramuscular injection.

4. METHOD(S) OF STERILIZATION: [redacted] of the lyophilized powder in vials and [redacted] sterilization of the prefilled syringes. The applicant has withdrawn the "Debioject" delivery system.

5. PHARMACOLOGICAL CATEGORY: Hormone agonist for the palliative treatment of prostate cancer

6. DRUG PRIORITY CLASSIFICATION: 1S

B. 1. DATE OF INITIAL SUBMISSION: June 24, 1996

2. DATE OF AMENDMENT: February 1, 2000

3. RELATED DOCUMENTS: Microbiologist's Reviews #1 (September 9, 1996) and #2 (March 21, 1997). The current amendment (February 1, 2000) states the submission consists of volume 2.2 (Chemistry, Manufacturing and Controls) of the December 16, 1999 amendment) and volume 1 of 2 from the February 11, 1999 submission (response to CMC, Biopharmaceutics, and Microbiology deficiencies) for the Microbiology reviewer.

4. ASSIGNED FOR REVIEW: February 16, 2000

C. REMARKS: The first and second microbiology reviews were done by another reviewer. This review will address only the responses to deficiency questions in Microbiologist's Review #2. The current submission responds to deficiencies provided in a FAX dated January 19, 2000. The cover letter notes that the "remaining items listed in the January 19, 2000 correspondence" will be submitted to FDA in the near future. Earlier submissions for this NDA used the tradename "decapeptyl" which was changed to Trelstar®. An undated jacket (possibly vol. 2.2 of the December 16, 1999 amendment) indicates the Debioject delivery system has been withdrawn.

D. CONCLUSIONS: Based on the withdrawal of the Debioject component, the submission is recommended for APPROVAL.

/S/ 5-5-2000
David Hussong, Ph.D.
5/5/00

cc:

Original NDA 20-715
HFD 160/Consult File
HFD 580/Division File
HFD 580/CSO/J. Best /T. Rumble
HFD 580/Chemist/ D. Lin /M. Rhee
HFD 805/D. Hussong

Drafted by: D. Hussong, 05/04/2000
R/D initialed by: P. Cooney

Filename, d:\nda\20-715rv3.DOC

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REVIEW FOR HFD-580
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF HFD-805

Microbiologist's Review #1 of NDA 20-715 Amendment
May 4, 1999

A. 1. **APPLICATION NUMBER:** 20-715 Amendment MAY 6 1999

APPLICANT: Debio Recherche Pharmaceutique SA
Route du Levant 146
CH-1920 Martigny
Switzerland

2. **PRODUCT NAMES:** Triptorelin (decapeptyl depot)

3. **DOSAGE FORM AND ROUTE OF ADMINISTRATION:** The depot suspension consists of decapeptyl sterile powder in a vial (3.75 mg of triptorelin peptide) and sterile diluent in a syringe (2 ml of WFI). The drug product is to be administered as a single monthly intramuscular injection.

4. **METHOD(S) OF STERILIZATION:** [redacted]

5. **PHARMACOLOGICAL CATEGORY:** The proposed indications are for palliative treatment of an advanced prostate cancer.

B. 1. **DATE OF INITIAL SUBMISSION:** June 24, 1996

2. **AMENDMENT:** February 11, 1999

3. **RELATED DOCUMENTS:** Response to request of additional information, 4/23/99.

4. **ASSIGNED FOR REVIEW:** March 10, 1999

5. **DATE OF CONSULT REQUEST:**

C. **REMARKS:**

The submission responds to microbiology deficiencies presented to the applicant as a result of Microbiologist's Review #2. The deficiencies were listed in the non-approvable letter dated June 26, 1997. The questions from the "List of Microbiology

Deficiencies and Comments" have been copied into the "Review Notes" section of this review and the responses are individually reviewed.

D. CONCLUSIONS:

The submission for the Decapeptyl vial (not the Debioject system) is recommended for approval for issues concerning microbiology.

Media fill on the assembly of the Debioject Delivery System has not been conducted, **the Applicant is requesting the approval of the Decapeptyl vial without the Debioject system.** Please note that such media fill data should be submitted for pre-approval review before Debioject system can be marketed.

/S/ — 5/4/99

Brenda Uratani, Ph.D.
Review Microbiologist

5/4/99

cc:

NDA 20-715 Amendment
HFD-580/ Div. File
HFD-805/ Uratani
HFD-580/Kish
drafted by: Brenda Uratani, 5/4/99
R/D initialed by P. Cooney, 5/4/99

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NDA 20-715 Amendment
Request for information

Pertaining to — sterilization of the Debiojects

1. Please specify if the residual — data in Appendix K are derived from the WFI or from WFI plus the Debioject device.
2. Please provide an outline on the procedures of how samples from the Debioject Delivery System are prepared for — determination.
3. Please show how the calculation is made to convert the — levels from mg/device (Griffith report on page 240) to ppm.

/S/

3/25/99

REVIEW FOR HFD-580
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF HFD-805

Microbiologist's Review # 2 of NDA 20-715
Response to FDA Request of Information
March 21, 1997

A. 1. APPLICATION NUMBER: 20-715

APPLICANT: Debio Recherche Pharmaceutique SA
Route du Levant 146
CH-1920 Martigny
Switzerland

2. PRODUCT NAMES: Triptorelin (decapeptyl depot)

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: The depot suspension consists of decapeptyl sterile powder (3.75 mg of triptorelin peptide) and sterile diluent (2 ml of WFI). The drug product is to be administered as a single monthly intramuscular injection.

4. METHOD(S) OF STERILIZATION: [redacted]

5. PHARMACOLOGICAL CATEGORY: The proposed indications for use are for palliative treatment of an advanced carcinoma of the prostate.

6. DRUG PRIORITY CLASSIFICATION:

B. 1. DATE OF INITIAL SUBMISSION: June 24, 1996

2. AMENDMENT: 2 submissions: November 19, 1996 and January 31, 1997.

3. RELATED DOCUMENTS:
DMFs: [redacted]
INDs: [redacted]
NDA: 20715

4. ASSIGNED FOR REVIEW: February 24, 1997

5. DATE OF CONSULT REQUEST: February 24, 1997

MAR 27 1997

C. REMARKS:

The submission responds to questions presented to the applicant as a result of Microbiologist's Review #1. The questions from the Microbiologist's Draft of Letter to the Applicant have been copied into the "Review Notes" section of this review and the responses are individually reviewed.

D. CONCLUSIONS:

The submission does not contain sufficient information to assure the sterility and safety of the drug product. The NDA is, therefore, not recommended for approval as submitted. Specific comments are provided in "Review Notes" and in the "Microbiologist's Draft Letter to Applicant".

/S/ 3/21/97

Brenda Uratani, Ph.D.
Review Microbiologist

/S/ 3/24/97

cc:

NDA 20-715
HFD-580/ Div. File
HFD-805 /Uratani
HFD-580/CSO/Dunson
drafted by: Brenda Uratani, 3/21/97
R/D initialed by P.Cooney, 3/21/97

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REVIEW FOR HFD-580
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF HFD-805

Microbiologist's Review # 1 of NDA 20-715
September 9, 1996

A. 1. **APPLICATION NUMBER:** 20-715

APPLICANT: Debio Recherche Pharmaceutique SA
Route du Levant 146
CH-1920 Martigny
Switzerland

2. **PRODUCT NAMES:** Triptorelin (decapeptyl depot)

3. **DOSAGE FORM AND ROUTE OF ADMINISTRATION:** The depot suspension consists of decapeptyl sterile powder (3.75 mg of triptorelin peptide) and sterile diluent (2 ml of WFI). The drug product is to be administered as a single monthly intramuscular injection.

4. **METHOD(S) OF STERILIZATION:** [redacted]

5. **PHARMACOLOGICAL CATEGORY:** The proposed indications for use are for palliative treatment of an advanced carcinoma of the prostate.

6. **DRUG PRIORITY CLASSIFICATION:** 1P

B. 1. **DATE OF INITIAL SUBMISSION:** June 24, 1996

2. **AMENDMENT:** none

3. **RELATED DOCUMENTS:**
DMFs: [redacted]
INDs: [redacted]

4. **ASSIGNED FOR REVIEW:** July 15, 1996

5. **DATE OF CONSULT REQUEST:** July 2, 1996

releasing hormone (LHRH) for the treatment of prostrate cancer. The drug product is to be manufactured by Debio Recherche Pharmaceutique in Martigny, Switzerland and packaged by Pharmacia & Upjohn Company in Kalamazoo, Michigan.

D. CONCLUSIONS:

The submission does not contain sufficient information to assure the sterility and safety of the drug product. It lacks validation protocols/data, and process specifications for the sterilization of the diluent and the Debioject delivery assembly. The NDA is, therefore, not recommended for approval as submitted. The sponsor should be provided with a copy of the FDA's "Guideline for Submitting Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products". Specific comments are provided in "Review Notes" and in the "Microbiologist's Draft Letter to Applicant".

/S/ 9/9/96

Brenda Uratani, Ph.D.

cc: /S/ 9/12/96

NDA 20-715
HFD-580/ Div. File
HFD-805 /Uratani
HFD-/CSO/Pauls
drafted by: Brenda Uratani, 9/9/96
R/D initialed by P.Cooney, 9/9/96

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

Statistical Review of Stability Protocol is not applicable for this drug product.

Stability addressed in
chem review #3 dated
5/19/00