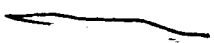


CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-197

MICROBIOLOGY REVIEW(S)

REVIEW FOR HFD-580
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW #2 OF DMF —
20 July 2000

- A. 1. DMF —
In support of NDA 21-197
DMF Holder:

2. AUTHORIZING PRODUCT NAME: Cetrotide® (cetorelix acetate for injection)
3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
The product is a sterile, lyophilized, injectable preparation. The pre-filled diluent syringes are to be packaged with the drug product.
4. METHODS OF STERILIZATION:
The product is aseptically filled. The prefilled diluent syringes are sterilized.
5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION:
The drug product is indicated for the prevention of premature ovulation undergoing controlled ovarian stimulation.
- B. 1. DATE OF INITIAL SUBMISSION: 28 October 1999
2. DATE OF AMENDMENT: 20 June 2000 (Subject of this Review)
3. RELATED DOCUMENTS: NDA 21-197
4. ASSIGNED FOR REVIEW: 30 June 2000
5. REMARKS: This DMF review was made in conjunction with review of NDA 21-197.

D. CONCLUSIONS: Data and descriptions in the DMF were found adequate to support product approval (NDA 21-197, Cetrotide®).

151
~~Paul Stinavage, Ph.D.~~ 20 July 2000
TAC 7/21/00

cc: Original DMF ➤
HFD-580/J. Best/T. Rumble/Div. File
HFD-805/Consult File/Stinavage

Drafted by: P. Stinavage, 20 July 2000
R/D initialed by P. Cooney

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APR 19 2000

REVIEW FOR HFD-580
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGISTS REVIEW OF DMF
11 April 2000

A. 1.

In support of NDA 21-197
DMF Holder:

- 2. AUTHORIZING PRODUCT NAME: Cetrotide® (cetorelix acetate for injection)
- 3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
The product is a sterile, lyophilized, injectable preparation. The pre-filled diluent syringes are to be packaged with the drug product.
- 4. METHODS OF STERILIZATION:
The product is aseptically filled. The prefilled diluent syringes are sterilized.
- 5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION:
The drug product is indicated for the prevention of premature ovulation undergoing controlled ovarian stimulation.

B.

- 1. DATE OF INITIAL SUBMISSION: 28 October 1999
- 2. DATE OF AMENDMENT: (none)
- 3. RELATED DOCUMENTS: NDA 21-197
- 4. ASSIGNED FOR REVIEW: 10 November 1999
- 5. REMARKS: This DMF review was made in conjunction with review of NDA 21-197.

D. CONCLUSIONS: Data and descriptions in the DMF were found inadequate to support product approval (NDA 21-197, Cetrotide®). Specific comments are provided in "E. Review Notes" and "List of Microbiology Deficiencies".

PS
~~Paul Stinavage, Ph.D.~~ 11 Apr. 2000
JK 4/19/00

cc: Original DMF —
HFD-580/J. Best/T. Rumble/Div. File
HFD-805/Consult File/Stinavage

Drafted by: P. Stinavage, 11 April 2000
R/D initialed by P. Cooney

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Commercial Information

NDA 21-197
Cetrotide™ (cetrotorelix acetate for injection)
ASTA Medica, Inc.

Environmental Assessment Review is Not Applicable for this NDA

*Categorical exclusion acceptable -
see chem review #1*

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CETRORELIX FOR INJECTION

CHEMISTRY, MANUFACTURING AND CONTROLS

Title: *IV. Environmental Impact Analysis Report*

We are requesting a categorical exclusion under 21 CFR 25.31(b). The approval of this application will increase the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion (ppb). In addition, the use and disposal of Cetorelix Acetate in Cetorelix for injection will be below 1 part per billion. To the best of our knowledge, no extraordinary conditions exist.

It is expected that about 10 kg per year of Cetorelix acetate will be shipped to the US. Based on this estimate, the calculated EIC is < 0.00023 ppb, or approximately 4000 times below the limit of 1 ppb, which justifies a categorical exclusion.

BEST POSSIBLE COPY

Vial Label

REVIEW FOR HFD-580
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW #2 OF NDA 21-197
20 July 2000

JUL 21 2000

- A.1. NDA 21-197
APPLICANT: ASTA Medica, Inc.
890 East Street
Tewksbury, MA 01876-1496
2. PRODUCT NAME: Cetrotide® (cetrotorelix acetate for injection)
3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
The product is a sterile, lyophilized injectable preparation.
4. METHODS OF STERILIZATION:
The product is aseptically filled.
5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION:
The drug product is indicated for the prevention of premature ovulation in patients undergoing controlled ovarian stimulation.
- B. 1. DATE OF INITIAL SUBMISSION: 28 October 1999
2. DATE OF AMENDMENT: 19 June 2000 (Subject of this Review)
3. RELATED DOCUMENTS: _____
.....
4. ASSIGNED FOR REVIEW: 23 June 2000
- C. REMARKS: The product will be manufactured by:

ASTA Medica AG
Pharmaceutical Production
Kantstrasse 2
D-33790 Halle/Kunsebeck
Germany

The product is manufactured in two strengths and packaged in two different vial sizes:

- The 0.25 mg product strength is packaged in a 2 mL colorless vial closed with a 1⁰
- The 3 mg product strength is packaged in a colorless 4 mL vial closed with a

D. CONCLUSIONS: The application is recommended for approval on the basis of sterility assurances. Deficiencies identified in the Drug Master File () have also been resolved separately.

151
20 July 2000
Paul Stinavage, Ph.D.
The
7/21/00

cc: Original NDA 21-197
HFD-580/J. Best/T. Rumble/Div. File
HFD-805/Consult File/Stinavage

Drafted by: P. Stinavage, 20 July 2000
R/D initialed by P. Cooney

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Best
APR 19 2000

REVIEW FOR HFD-580
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGISTS REVIEW OF NDA 21-197
11 April 2000

A.1. NDA 21-197

APPLICANT: ASTA Medica, Inc.
890 East Street
Tewksbury, MA 01876-1496

2. PRODUCT NAME: Cetrotide® (cetorelix acetate for injection)

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
The product is a sterile, lyophilized injectable preparation.

4. METHODS OF STERILIZATION:
The product is aseptically filled.

5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE
INDICATION:

The drug product is indicated for the prevention of premature ovulation
in patients undergoing controlled ovarian stimulation.

B. 1. DATE OF INITIAL SUBMISSION: 28 October 1999

2. DATE OF AMENDMENT: (none)

3. RELATED DOCUMENTS: _____

4. ASSIGNED FOR REVIEW: 11 November 1999

C. REMARKS: The product will be manufactured by:

ASTA Medica AG
Pharmaceutical Production
Kantstrasse 2
D-33790 Halle/Kunsebeck
Germany

The product is manufactured in two strengths and packaged in two different vial sizes:

- The 0.25 mg product strength is packaged in a 2 mL colorless vial closed with a _____
- The 3 mg product strength is packaged in a colorless 4 mL vial closed with a _____

D. CONCLUSIONS: The application is approvable upon resolution of microbiology concerns. Specific comments are provided in "E. Review Notes" and "List of Microbiology Deficiencies". Deficiencies were also identified in the Drug Master File (_____) . DMF deficiencies are being supplied separately to the DMF holder.

PS

Paul Stinavage, Ph.D.

11 April 2000

PTC 4/19/00

cc: Original NDA 21-197
HFD-580/J. Best/T. Rumble/Div. File
HFD-805/Consult File/Stinavage

Drafted by: P. Stinavage, 11 April 2000
R/D initialed by P. Cooney

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NDA 21-197
Cetrotide™ (cetrotorelix acetate for injection)
ASTA Medica, Inc.

Stability Statistical Review is Not Applicable for this NDA

*Stability review included in chem
review #1*

FDA CDER EES
 ESTABLISHMENT EVALUATION REQUEST
 DETAIL REPORT

Application: NDA 21197/000
 Stamp: 29-OCT-1999
 Regulatory Due: 29-AUG-2000
 Applicant: ASTA MEDICA (US)
 890 EAST ST
 TEWKSBURY, MA 018761496
 Priority: 1S
 Org Code: 580

Action Goal:
 District Goal: 30-JUN-2000
 Brand Name: CETROTIDE (CETRORELIX ACETATE FOR INJECTI
 Estab. Name:
 Generic Name: CETRORELIX ACETATE FOR INJECTION
 Dosage Form: (FOR INJECTION)
 Strength: 0.25 MG AND 3 MG

Application Comment:

FDA Contacts: J. BEST (HFD-580) 301-827-4260 , Project Manager
 S. TRAN (HFD-580) 301-827-4260 , Review Chemist
 M. RHEE (HFD-580) 301-827-4237 , Team Leader

Overall Recommendation: ACCEPTABLE on 18-JUL-2000 by M. EGAS (HFD-322) 301-594-0095

Establishment: 9611095

ASTA MEDICA AG
 D-4802
 HALLE-KUENSEBECK, , GM

DMF No: AADA:
 Responsibilities: FINISHED DOSAGE MANUFACTURER
 Profile: SVS OAI Status: NONE
 Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	14-DEC-1999				TRANS
SUBMITTED TO DO	15-DEC-1999	GMP			FERGUSONS
ASSIGNED INSPECTION	20-DEC-1999	GMP			ADAMSS
INSPECTION SCHEDULED	09-APR-2000		07-APR-2000		IRIVERA
INSPECTION PERFORMED	09-APR-2000		07-APR-2000		IRIVERA
DO RECOMMENDATION	18-JUL-2000			ACCEPTABLE INSPECTION	EGASM
NO FDA-483 ISSUED					
OC RECOMMENDATION	18-JUL-2000			ACCEPTABLE	EGASM
				DISTRICT RECOMMENDATION	

Establishment: _____

DMF No: AADA:
 Responsibilities: _____
 Profile: CSN OAI Status: NONE
 Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	14-DEC-1999				TRANS
SUBMITTED TO DO	15-DEC-1999	GMP			FERGUSONS
DO RECOMMENDATION	20-DEC-1999			ACCEPTABLE	ADAMSS
OC RECOMMENDATION	20-DEC-1999			BASED ON FILE REVIEW ACCEPTABLE	ADAMSS
				DISTRICT RECOMMENDATION	

Establishment: _____

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

DMF No: _____ AADA:
 Responsibilities: DRUG SUBSTANCE MANUFACTURER
 Profile: CSN OAI Status: NONE
 Estab. Comment: _____

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	14-DEC-1999				TRANS
SUBMITTED TO DO	15-DEC-1999	GMP			FERGUSONS
DO RECOMMENDATION	20-DEC-1999			ACCEPTABLE	ADAMSS
OC RECOMMENDATION	20-DEC-1999			BASED ON FILE REVIEW ACCEPTABLE	ADAMSS
				DISTRICT RECOMMENDATION	

Establishment: _____

DMF No: _____ AADA:
 Responsibilities: _____
 Profile: _____ OAI Status: NONE
 Estab. Comment: _____

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	14-DEC-1999				TRANS
SUBMITTED TO DO	15-DEC-1999	GMP			FERGUSONS
DO RECOMMENDATION	20-DEC-1999			ACCEPTABLE	ADAMSS
OC RECOMMENDATION	20-DEC-1999			BASED ON FILE REVIEW ACCEPTABLE	ADAMSS
				DISTRICT RECOMMENDATION	

APPEARS THIS WAY
ON ORIGINAL

NDA 21-197
Cetrotide™ (cetrotorelix acetate for injection)
ASTA Medica, Inc.

Methods Validation is Pending for this NDA

**APPEARS THIS WAY
ON ORIGINAL**