CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-197

CHEMISTRY REVIEW(S)

JUL 24 2000

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS (HFD-580)

Review of Chemistry, Manufacturing, and Controls

NDA #: 21-197
CHEMISTRY REVIEW #: 3

DATE REVIEWED: 24-JUL-2000
REVIEWER: Suong Tran/Moo-Jhong Rhee

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMENDMENT	19-JUN-2000		
AMENDMENT	29-JUN-2000	2-JUN-2000	5-JUN-2000
AMENDMENT	11-JUL-2000	24-JUL-2000	24-JUL-2000
AMENDMENT	17-JUL-2000	18-JUL-2000	19-JUL-2000

NAME & ADDRESS OF APPLICANT: ASTA Medica, Inc.
890 East Street
Tewksbury, MA 01876-1496

DRUG PRODUCT NAME

Proprietary:	Cetrotide™ 0.25 mg Cetrotide™ 3 mg
Established:	cetrorelix acetate for injection
Code Name/#:	SB-075 acetate, D-20761 (acetate salt)
Chem. Type/Ther. Class:	1S

PHARMACOL. CATEGORY/INDICATION: LHRH antagonist for the prevention of premature ovulation in patients undergoing ovarian stimulation.

DOSAGE FORM: sterile powder to be reconstituted with Sterile Water for Injection

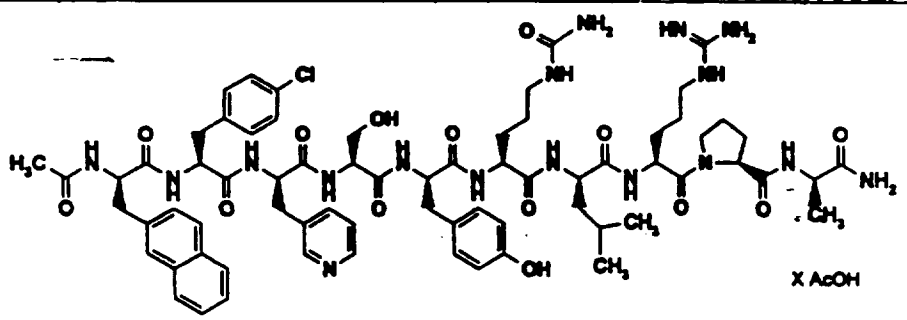
STRENGTHS: 0.25 mg to be reconstituted in 1.0 mL SWFI or
3 mg to be reconstituted in 3.0 mL SWFI

ROUTE OF ADMINISTRATION: subcutaneous injection

DISPENSED: __X__ Rx _____ OTC

SPECIAL PRODUCTS: _____ Yes __X__ No

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



Ac-D-Nal-D-p-Cl-Phe-D-Pal-Ser-Tyr-D-Cit-Leu-Arg-Pro-D-Ala-NH_2.
IUPAC: Acetyl-D-2-naphthylalanyl-D-4-chlorophenylalanyl-D-pyridylalanyl-seryl-tyrosyl-D-citrulyl-leucyl-arginyl-prolyl-D-alaninamide.
Molecular formula: $C_{70}H_{82}ClN_{17}O_{14}$ x AcOH
Molecular weight: 1431.06 (free base)
CAS # 130143-01-0

SUPPORTING DOCUMENTS:

- See Chemistry Review #2

RELATED DOCUMENTS:

- NDA 21-197 Microbiology Review dated 20-July-2000
- DMF 8084 Microbiology Review dated 20-July-2000.

CONSULTS:

- The Office of Compliance recommended "Acceptable" for [redacted] on 20-DEC-1999. The inspection of the remaining facility, Asta Medica AG, was performed on 9-APR-2000. On July 18, 2000, an overall recommendation of "Acceptable" was made for this NDA.
- OPDRA review of the proprietary name Cetrotide™ was completed on 19-APR-2000 and the name is found to be acceptable. Because the review was completed more than 90 days before the action due date, another follow-up consult review request was made by the Project Manager (J. Best) on 8-JUN-2000 and also found acceptable on 28-Jun-2000 (e-mail from Jerry Phillips to Jeanine Best).
- Microbiology reviews of the NDA and of DMF [redacted]) found both to be deficient. The sponsor responded to those deficiencies noted in NDA and DMF, and Microbiologist's reviews dated July 20, 2000 indicate that their responses are all satisfactory.

REMARKS/COMMENTS:

- In Chemistry Review #2, there was one issue on expiry date for 0.25mg dosage form.

  The Agency's proposal on the expiry date described in Chemistry Review #2 was conveyed to the sponsor through a t-con, and an amendment dated June 29, 2000 was submitted accepting 24-month expiry date at 2-8°C for 0.25mg without changing impurity specification.

- Established name: The applicant submitted an application to the USAN council on 17-MAY-2000 for the name "cetrorelix acetate" and it was accepted on June 28, 2000 according to the amendment dated July 11, 2000 (fax).

- Final mock-ups of labels were submitted in the amendment dated July 17, 2000, which are deemed satisfactory.

CONCLUSION & RECOMMENDATIONS:
Now all outstanding CMC issues are clarified and, therefore, from the Chemistry perspective, NDA 21-197 may be approved.

cc:
NDA 21-197:
HFD-580/Division File
HFD-580/JBest/STran/MRhee
HFD-820/JGibbs/SKoepke

/S/ 7/24/00
Suong T. Tran, Ph.D.
Review Chemist

/S/ 7/24/00
Moo-Jhong Rhee, Ph.D.
Team Leader

R/D Init by:
Filename: NDA21197\original v3.doc

APPEARS THIS WAY
ON ORIGINAL

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

4 pages

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 DISTRICT RECOMMENDATION	EGASM

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 BASED ON FILE REVIEW	ADAMSS
OC RECOMMENDATION	20-DEC-1999			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS

Establishment: ———

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

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
				BASED ON FILE REVIEW	
OC RECOMMENDATION	20-DEC-1999			ACCEPTABLE	ADAMSS
				DISTRICT RECOMMENDATION	

Establishment:

DMF No: AADA:
Responsibilities:
Profile: OAI Status: NONE
Estab. Comment:
)N. (on 14-DEC-1999 by S. TRAN (HFD-580) 301-827-4260)

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
				BASED ON FILE REVIEW	
OC RECOMMENDATION	20-DEC-1999			ACCEPTABLE	ADAMSS
				DISTRICT RECOMMENDATION	

APPEARS THIS WAY
ON ORIGINAL

JUL 13 2000

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS (HFD-580)

Review of Chemistry, Manufacturing, and Controls

NDA #: 21-197
CHEMISTRY REVIEW #: 2

DATE REVIEWED: 15-JUN-2000
REVIEWER: Suong Tran

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
AMENDMENT	1-JUN-2000	2-JUN-2000	5-JUN-2000

NAME & ADDRESS OF APPLICANT: ASTA Medica, Inc.
890 East Street
Tewksbury, MA 01876-1496

DRUG PRODUCT NAME

Proprietary:	Cetrotide™ 0.25 mg Cetrotide™ 3 mg
Established:	cetrorelix acetate for injection
Code Name/#:	SB-075 acetate, D-20761 (acetate salt)
Chem. Type/Ther. Class:	1S

PHARMACOL. CATEGORY/INDICATION: LHRH antagonist for the prevention of premature ovulation in patients undergoing ovarian stimulation.

DOSAGE FORM: sterile powder to be reconstituted with Sterile Water for Injection

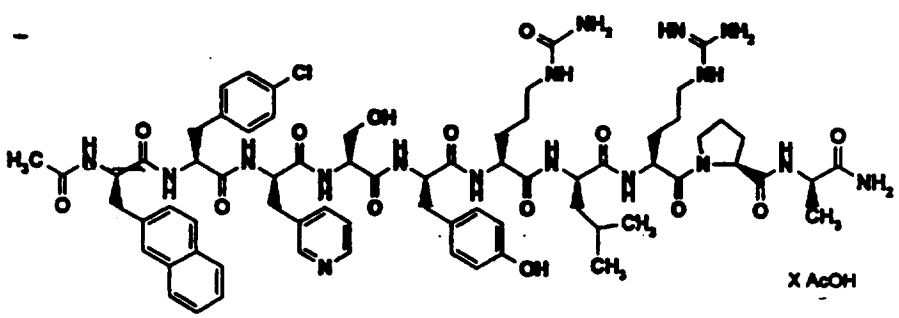
STRENGTHS: 0.25 mg to be reconstituted in 1.0 mL SWFI or
3 mg to be reconstituted in 3.0 mL SWFI

ROUTE OF ADMINISTRATION: subcutaneous injection

DISPENSED: X Rx _____ OTC

SPECIAL PRODUCTS: _____ Yes X No

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



Ac-D-Nal-D-p-Cl-Phe-D-Pal-Ser-Tyr-D-Cit-Leu-Arg-Pro-D-Ala-NH_2.
IUPAC: Acetyl-D-2-naphthylalanyl-D-4-chlorophenylalanyl-D-pyridylalanyl-seryl-tyrosyl-D-citrulyl-leucyl-arginyl-prolyl-D-alaninamide.

Molecular formula: $C_{70}H_{82}ClN_{17}O_{14}$ x AcOH
Molecular weight: 1431.06 (free base)
CAS # 130143-01-0

SUPPORTING DOCUMENTS:

Type/Number	Subject	Holder	Status	Review date	Letter date
		ASTA	Active	Not applicable	Not applicable
			Deficient	19-APR-2000 (P. Stivanage)	2-MAY-2000
			Adequate	13-NOV-1998 (M. Adams)	Not applicable

RELATED DOCUMENTS:

- Chemistry Review #1 dated 30-MAR-2000.
- Chemistry IR letter dated 4-APR-2000.
- NDA 21-197 Microbiology Review dated 19-APR-2000
-
- OPDRA Review of the proprietary name Cetrotide™ dated 19-APR-2000.

CONSULTS:

- The Office of Compliance recommended "Acceptable" for on 20-DEC-1999. The inspection of the remaining facility, Asta Medica AG, was performed on 9-APR-2000. No final recommendation on Asta Medica AG has been made.
- OPDRA review of the proprietary name Cetrotide™ was completed on 19-APR-2000. The name is found to be acceptable. Because the review was completed more than 90 days before the action due date, another consult review request was made by the Project Manager (J. Best) on 8-JUN-2000.
- Microbiology reviews of the NDA and of found both to be deficient. FDA is currently awaiting responses from the NDA applicant and the DMF holder.

REMARKS/COMMENTS:

- The applicant submitted an application to the USAN council on 17-MAY-2000 for the name "cetrorelix acetate". A copy of the application is provided in Attachment 1. The applicant requested an expedited review by the council on 26-JUN-2000. Per FDA Labeling and Nomenclature Committee (see attached email from Dan Boring), this is sufficient for not holding up the NDA approval process.
- As discussed in Question and Answer 9 of the Chemist's Review Notes, the drug substances are shown to be comparable. Stability data for the two resulting 3 mg drug products show that they are also comparable. Therefore, the proposed expiry of two years at room temperature is acceptable for the 3 mg dose. This expiry of two years at room temperature is supported by the full real-time stability data (24-month at 25 °C/60% RH) for the pilot-scale lots and by the 12-month at 25 °C/60% RH data + 6-month accelerated data for the to-be-marketed product.
- As discussed in Question and Answer 9 of the Chemist's Review Notes, the drug substances are comparable. However, 9-month stability data at 25 °C/60% RH and 6-month accelerated data for the two resulting 0.25 mg drug products show that the 0.25 mg drug products are not comparable. Therefore, the proposed expiry of two years at room temperature is not acceptable

for the 0.25 mg dose. Based on all available stability data, the expiration dating period for the 0.25 mg dose should be **either** two years at 2-8 °C (no change in specifications) **or** one year at room temperature with changes in shelf life specifications: from 90-105% to 88-105% for Cetrorelix Content, from NMT 1.5% to NMT 2.5% for D-21739, and from NMT 2.5% to NMT 3.5% for Total Impurities.

- Regarding the labeling (package inserts and container labels), the applicant has made all the revisions as suggested by FDA in the Chemistry IR letter. From the Chemistry perspective, the labeling is satisfactory.

CONCLUSION & RECOMMENDATIONS:

From the Chemistry perspective, NDA 21-197 is approvable pending the resolution of issues discussed in the CONSULTS section above and in the attached (draft) Information Request letter.

cc:
NDA 21-197:
HFD-580/Division File
HFD-580/JBest/STran/MRhee
HFD-820/JGibbs/SKoepke

/S/ JUN 2000
Suong T. Tran, Ph.D.
Review Chemist

/S/ 6/26/00
Moo-Jhong Rhee, Ph.D.
Team Leader

R/D Init by:
Filename: NDA21197\original v3.doc

APPEARS THIS WAY
ON ORIGINAL

Draft Information Request Letter

The review of the CMC information submitted in the 1-JUN-2000 amendment has been completed and the following comments should be conveyed to the applicant for additional information:

1. [redacted]

APPEARS THIS WAY
ON ORIGINAL

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

10 pages

MAR 30 2000

DIVISION OF REPRODUCTIVE AND UROLOGIC DRUG PRODUCTS (HFD-580)

Review of Chemistry, Manufacturing, and Controls

NDA #: 21-197
CHEMISTRY REVIEW #: 1

DATE REVIEWED: 23-MAR-2000
REVIEWER: Suong Tran

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	28-OCT-1999	29-OCT-1999	2-NOV-1999

NAME & ADDRESS OF APPLICANT: ASTA Medica, Inc.
890 East Street
Tewksbury, MA 01876-1496

DRUG PRODUCT NAME

Proprietary:	Cetrotide™ 0.25 mg Cetrotide™ 3 mg
Established:	cetrorelix acetate for injection
Code Name/#:	SB-075 acetate, D-20761 (acetate salt)
Chem. Type/Ther. Class:	1S

PHARMACOL. CATEGORY/INDICATION: LHRH antagonist for the prevention of premature ovulation in patients undergoing ovarian stimulation.

DOSAGE FORM: sterile powder to be reconstituted with Sterile Water for Injection

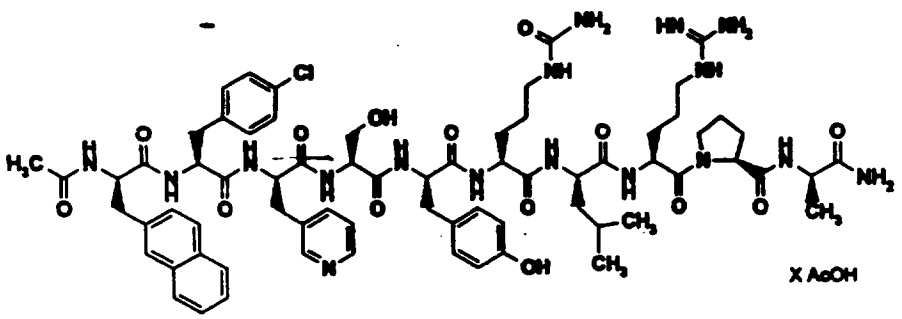
STRENGTHS: 0.25 mg to be reconstituted in 1.0 mL SWFI or
3 mg to be reconstituted in 3.0 mL SWFI

ROUTE OF ADMINISTRATION: subcutaneous injection

DISPENSED: X Rx _____OTC

SPECIAL PRODUCTS: _____Yes X No

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



Ac-D-Nal-D-p-Cl-Phe-D-Pal-Ser-Tyr-D-Cit-Leu-Arg-Pro-D-Ala-NH_2.
IUPAC: Acetyl-D-2-naphthylalanyl-D-4-chlorophenylalanyl-D-pyridylalanyl-seryl-tyrosyl-D-citrulyl-leucyl-arginyl-prolyl-D-alaninamide.

Molecular formula: $C_{70}H_{82}ClN_{17}O_{14}$ x AcOH
Molecular weight: 1431.06 (free base)
CAS # 130143-01-0

SUPPORTING DOCUMENTS:

Type/Number	Subject	Holder	Status	Review date	Letter date
		ASTA	Active	Not applicable	Not applicable
			Pending	Under review by Microbiology.	Under review by Microbiology.
		a	Adequate	13-NOV-1998 (M. Adams)	Not applicable

RELATED DOCUMENTS:
None

CONSULTS:

- The Office of Compliance recommended "Acceptable" for ' on 20-DEC-1999. The inspection of the remaining facility, Asta Medica AG, is currently ongoing.
- A review consult of the proposed propriety name was requested on 6-DEC-1999 via J. Best (PM) to OPDRA. The OPDRA review is currently ongoing.
- A Microbiology consult review was requested for the NDA (Sterilization Validation Package, Volume 19) in November of 1999 and for) in December of 1999 by J. Best (PM). The Microbiology reviews are currently ongoing.

REMARKS/COMMENTS:
NDA 21-197 is for cetrorelix acetate, a new molecular entity. Cetrorelix acetate consists of ten amino acids, including five in the non-natural D configuration. The decapeptide has ten chiral centers. No racemization has been found during synthesis. Synthesis of cetrorelix acetate is a solution-phase process. Three peptide fragments are synthesized and condensed to form a protected peptide. Deprotection and purification is by preparative HPLC. Cetrotide™ is a sterile powder for injection to be reconstituted with Sterile Water for Injection (SWFI) prior to administration. The two dosage strengths, 0.25 mg and 3 mg, are reconstituted with 1 mL and 3 mL SWFI, respectively. The inactive ingredient is mannitol, USP, used to adjust the isotonicity of the solution. The two dosage strengths, 0.25 mg and 3 mg, are packaged in 2 mL and 4 mL clear Type I glass vials, respectively, with a . One pack of product for distribution includes one vial of Cetrotide™, one pre-filled glass syringe containing 1 mL SWFI for the 0.25 mg dosage or 3 mL SWFI for the 3 mg dosage, one 20-gauge needle, one 27-gauge needle, and two alcohol swaps. For distribution there is also an available carton of seven packs of product. Stability of the drug product: expiry is proposed to be 24 months when stored below 25 °C for both dosage strengths.

CONCLUSION &RECOMMENDATIONS:
The NDA currently has incomplete information. Please issue an Information Request letter (refer to the attached Draft Letter).

cc:

Orig. NDA # 21-197
HFD-580/Division File
HFD-580/JBest/STran/MRhee
HFD-820/JGibbs/SKoepke

/S/ 3/28/2000

Suong T. Tran, Ph.D.
Review Chemist

R/D Init by:

/S/ 3/30/00

Moo-Jhong Rhee, Ph.D.
Team Leader

Filename: NDA21197\original v2.doc

APPEARS THIS WAY
ON ORIGINAL

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

49 pages

Have all DMF References been identified? YES

Number	Description	Holder	LOA	Status
			01-SEP-1999	Under review
			04-FEB-1998	Under review

DRUG PRODUCT NAME

Proprietary: Cetrotide™
Nonproprietary/USAN: cetrorelix acetate

APPLICANT:

ASTA Medica, Inc.

PHARMACOL. CATEGORY/INDICATION: LHRH antagonist for the prevention of premature ovulation in patients undergoing ovarian stimulation.

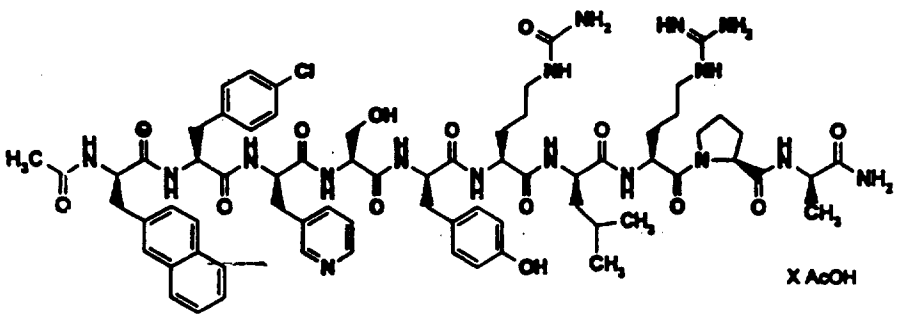
DOSAGE FORM: sterile powder to be reconstituted with SWFI

STRENGTHS: 0.25 mg to be reconstituted in 1.0 mL SWFI or
3 mg to be reconstituted in 3.0 mL SWFI

ROUTE OF ADMINISTRATION: subcutaneous injection

DISPENSED: __X__ Rx _____ OTC

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



Ac-D-Nal-D-p-Cl-Phe-D-Pal-Ser-Tyr-D-Cit-Leu-Arg-Pro-D-Ala-NH_2.
IUPAC: Acetyl-D-2-naphthylalanyl-D-4-chlorophenylalanyl-D-pyridylalanyl-seryl-tyrosyl-D-citrulyl-leucyl-arginyl-prolyl-D-alaninamide.
Molecular formula: $C_{70}H_{82}ClN_{17}O_{14}$ x AcOH
Molecular weight: 1431.06 (free base)
CAS # 130143-01-0

A. DRUG SUBSTANCE

- New molecular entity
- Manufacturers:
  (1)
  (2
- Cetrorelix acetate consists of ten amino acids, including five in the non-natural D configuration. The decapeptide has ten chiral centers. No racemization has been found during synthesis.
- Synthesis of cetrorelix acetate is process. Three peptide fragments are synthesized and condensed to form a protected peptide. Deprotection and purification is by preparative HPLC.
- The three peptide fragments and the resulting heptamer and decamer are characterized by and is also used to confirm the amino acid sequences. The structure of cetrorelix is analyzed by , and

B. DRUG PRODUCT

- Cetrotide™ is a sterile powder for injection. The two dosage strengths, 0.25 mg and 3 mg, are reconstituted with 1 mL and 3 mL SWFI, respectively. The inactive ingredient is mannitol, USP, used to adjust the isotonicity of the solution.
- Manufacturer:
  A) Manufacturing, testing and packaging of the drug product: ASTA Medica AG.
  B) Manufacturing and testing of SWFI pre-filled syringes and packaging of the syringes with the drug product containers:
  C) Final release: ASTA Medica AG.
- Stability of the drug product: expiry is proposed to be 24 months when stored below 25 °C for both dosage strengths. Data are available for three production lots (up to 6 months of storage) and three pilot lots (up to 24 months of storage) under these conditions: 8 °C, 25 °C/60% RH, 30 °C/70% RH, and 40 °C/70% RH.