CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-197

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

David Baird, M.D.
Department of Obstetrics & Gynecology
Center for Reproductive Biology
37 Chalmers Street
Edinburgh EH3 9EW
United Kingdom

AUG - 4 2000

Dear Dr. Baird:

Between April 10 and April 13, 2000, Ms. Brunilda Torres and Dr. Roy Blay representing the U. S. Food and Drug Administration (FDA), inspected your conduct of a clinical study (Protocol #D-20761-3010) of the investigational drug Cetrotide™ (cetrorelix acetate for injection). You performed this study for ASTA Medica, Inc. This inspection is part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of these studies have been protected.

At the conclusion of the inspection, Ms. Torres and Dr. Blay met with you to discuss the items listed on the Form FDA 483, Inspectional Observations. We have reviewed the inspection report and your written response, dated April 19, 2000, to the items on the Form FDA 483.

We understand that your study was not conducted under a U.S. Investigational Drug Application (IND). For your future reference, however, we offer our comments in the same manner as we would if the study had been performed under a U.S. IND. Our findings are summarized below:

1. You did not adhere to the study protocol.

   Subject #s 020 and 026 had progesterone levels exceeding 2 ng/mL on Day 1 of HMG treatment. This was a violation of the protocol which required that progesterone levels not exceed 1 ng/mL.

2. Procedures for obtaining informed consent were inadequate.

   According to your letter of April 19, 2000, the Ethics Committee approved the local version of the informed consent form. Our inspection revealed that subject #s 313, 021, and 036 signed only the sponsor version of the form.

3. You failed to maintain adequate and accurate records.

   Original laboratory testing reports (printouts) for hCG, LH, and E2 were available for only five of the study subjects and covered only a limited period of the study. The remaining original reports were destroyed after one year according to the testing laboratory's established procedures.

4. You failed to maintain adequate and accurate records regarding drug disposition.

   Destruction of unused study drug at the site was not documented, therefore it was not possible to make a full accounting of the disposition of all study drug.

We appreciate the cooperation shown Ms. Torres and Dr. Blay during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

/S/ M.D.

John R. Martin, M.D.
Branch Chief
Good Clinical Practice I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Suite 103
Rockville, Maryland 20855

APPEARS THIS WAY
ON ORIGINAL

cc:
HFA-224
HFD-580/Doc. Rm. NDA 21-197
HFD-580/Review Div. Dir.
HFD-580/Best
HFD-580/Willett
HFD-45/Reading File
HFD-46/Chron File
HFD-46/GCP File # 010141
HFD- 46/Blay
HFD-46/Huff
HFD-46/Martin
HFR-SE250/Chappell
HFR-SE250/Torres

CFN: #

Field Classification: VAI

Headquarters Classification:

_____1)NAI
__x__2)VAI no response required
_____3)VAI-R response requested
_____4)VAI-RR adequate response received prior to issuance of VAI-R letter
_____5)OAI-WL warning letter
_____6)OAI-NIDPOE

O:/blay/baird.rab
drafted/rab/7.18.00
reviewed:/JM
final:mgk 7/31/00

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Note to Review Division and DSI Recommendation:

The field investigators inspected the study-related records for 14 of the 61 subjects enrolled in protocol # D-20761-3010 at Dr. Baird's site. The data appear acceptable for use in support of drug claims.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: August 2, 2000

TO: Jeannine Best, Regulatory Project Manager
Gerald Willett, M.D. Clinical Reviewer
Division of Reproductive and Urologic Drug Products, HFD-580

THROUGH: John R. Martin, M.D.
Branch Chief
Good Clinical Practice I, HFD-46
Division of Scientific Investigations

FROM: Roy Blay, Ph.D.,
Senior Regulatory Review Officer
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-197

APPLICANT: ASTA Medica, Inc.

DRUG: Cetrotide™ (cetrorelix acetate for injection)

THERAPEUTIC CLASSIFICATION: 1(S)

INDICATION: Treatment of premature ovulation in women undergoing controlled ovarian stimulation

REVIEW DIVISION GOAL DATE: July 18, 2000
PDUFA DATE: August 29, 2000

I. BACKGROUND:

The goal of inspection included validation of submitted data and compliance of study activities with Federal regulations and good clinical practices. Among the study elements reviewed for compliance were subject record accuracy, appropriate informed consent, appropriate use of inclusion/exclusion criteria, adherence to protocol, randomization procedures, and documentation of serious adverse events. The indication for this NDA is treatment of premature ovulation in women undergoing controlled ovarian stimulation.

The Edinburgh, Scotland site was not one of the original sites selected for inspection. Initially, the study site in Glasgow, Scotland, under Dr. Richard Fleming, was selected for inspection. In the process of arranging the inspection, it was discovered that the ultrasound diary from 1996 had been misplaced. The two individuals responsible for the documentation died, and it was not possible to locate this data without their assistance. This information was conveyed to FDA via the Letter of Assurance signed by Dr. Fleming.

This situation was discussed within DSI and with Dr. Willett from HFD-580. It was decided to select another site for inspection rather than inspect a site with known documentation deficiencies. As a result, DSI is unable to verify/assess the study data submitted by the Glasgow site. DSI recommends that the Review Division consider excluding the data from the Glasgow site from the efficacy analysis.

II. RESULTS (by site):

NAME	CITY, STATE/COUNTRY	ASSIGNED DATE	RECEIVED DATE	CLASSIFICATION/ FILE NUMBER
Jarl Kahn	Copenhagen, DK	3/1/00	6/15/00	VAI/010111
David Baird	Edinburgh, UK	2/2/00	7/20/00	VAI/010141
Rene Frydman	Clamart, FR	5/15/00	*	NAI/*

*The EIR for this inspection has not been received as of 7/28/00; however, I have spoken with the FDA inspector, Ms. Mary Carden, who informed me that the inspection went very well and no 483 was issued. Review of the EIR is unlikely to change the NAI classification of this inspection.

Site #1
Protocol #D-20761-3010
Jarl Kahn, M.D., Ph.D.
Ciconia Fertility Clinic
Frydendalsvej 5
Copenhagen, Denmark
Acceptable

a. The field investigators inspected the study-related records for 18 of the 60 subjects at Dr. Kahn's site.

b. There were no limitations on the inspection.

c. A 483 was issued because the investigator committed minor violations of the study protocol, and the "Patient Information and Consent Form" used by the investigator lacked certain elements required by U.S. regulation (though not necessarily required by other applicable international regulations).

Site #2
Protocol #D-20761-3010
David Baird, M.D.
Department of Obstetrics & Gynecology
Center for Reproductive Biology
37 Chalmers Street
Edinburgh EH3 9EW
United Kingdom
Acceptable

a. The field inspector inspected the records of 14 of the 61 subjects enrolled at Dr. Baird's site.

b. There were no limitations on the inspection.

c. A 483 was issued. Deficiencies included violations of the study protocol, inadequate informed consent procedures, failure to maintain adequate and accurate study records, and failure to maintain adequate and accurate records regarding study drug disposition.

Site #3
Protocol #D-20761-3030
Prof. Dr. Rene Frydman
Hopital Antoine Beclere
157, rue de la Porte-de-Trivaux
92140, Clamart, France
Acceptable* (See note above)

a. The field investigator has completed her inspection of Dr. Frydman's site.

b. There were no limitations on the inspection.

c. No 483 was issued. The inspection was unremarkable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Overall, no violations were observed that would affect the reliability or integrity of the data submitted in support of this NDA.

Follow-up action: None needed at this time.

/S/ 8/2/00

Roy Blay, Ph.D., Clinical Reviewer
DSI/GCPBI

CONCURRENCE:

/S/ MD

John R. Martin, M.D.
Branch Chief
Good Clinical Practice I, HFD-46
Division of Scientific Investigations

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DISTRIBUTION:

NDA 21-197
HFD-45/Division File
HFD-46/Program Management Staff (electronic copy)
HFD-580/Best
HFD-580/Willett
HFD-46/Blay
HFD-46/Huff
HFD-46/Martin
HFD-46/GCP File #s 010111, 010141, and
HFD-46/Reading File

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

45 pages

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	21197	**Trade Name:**	CETROTIDE(CETRORELIX ACETATE FOR INJECTI
Supplement Number:		**Generic Name:**	CETRORELIX ACETATE FOR INJECTION
Supplement Type:		**Dosage Form:**	FIJ
Regulatory Action:	AP	**Proposed Indication:**	The prevention of premature premature LH surges in women undergoing controlled ovarian stimulation

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, Pediatric content not necessary because of pediatric waiver

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)

____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy Does Not Apply

Formulation Status

Studies Needed

Study Status

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, JEANINE BEST

/S/ 8/11/03

Signature Date

Electronic Mail Message

Date: 6/28/00 8:18:50 AM
From: Jerry Phillips (PHILLIPSJ)
To: Jeanine Best (BESTJ)
Cc: Sammie Beam (BEAMS)
Cc: Suong Tran (TRANS)
Subject: Cetrotide

Jeanine:

OPDRA has re-reviewed the proposed proprietary name Cetrotide (Cetrotide for Injection) for NDA 21-197 and have no objections to its use and approval. If you have any further questions, please feel free to call Sammie. Thanks.

Jerry Phillips
Associate Director, OPDRA

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Number of Pages Redacted 278 pages

from consecutive sections (13) of draft labeling

❖❖❖

Draft Labeling (not releasable)

1) 16 pages
2) 17 pages
3) 17 pages
4) 16 pages
5) 18 pages
6) 15 pages
7) 16 pages
8) 16 pages
9) 16 pages
10) 15 pages
11) 14 pages
12) 31 pages
13) 71 pages

278 pages

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

There are no Phase 4 Commitments.

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

DRUDP and Office Label Revisions, August 10, 2000

APPEARS THIS WAY
ON ORIGINAL

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

DRUDP Labeling Revisions, June 21, 2000

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

DRUDP and Office Label Revisions, August 8, 2000

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

DRUDP Labeling Revision, 14 July 2000

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

DRUDP Label Revisions, 7/11/00

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

DRUDP Label Revision, 7/13/00.

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

Unmarked Revised Label from the sponsor. 18 July 2000

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

Sponsor Proposed Revised Label, July 14, 2000.

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

Sponsor Proposed Labeling Revisions, June 30, 2000

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

Sponsor Revised Labeling, Two Doses Combined In One Label, June 9, 2000

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

Sponsor Original Label, October 28, 1999

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

Mock up of Labeling dated 17 July 2000

Electronic Mail Message

Date: 6/8/00 10:22:49 AM
From: Jeanine Best (BESTJ)
To: Sammie Beam (BEAMS)
Cc: Suong Tran (TRANS)
Subject: NDA 21-197 Cetrotide

Hi Sammie,
OPDRA approved the proprietary name Cetrotide for NDA 21-197 (OPDRA Consult # 00-0007), on April 18, 2000. We are now within 90 days of the PDUFA date for approval, (August 29, 2000). Is the name Cetrotide still acceptable?
Thanks,
Jeanine Best, PM
DRUDP, HFD-580

APPEARS THIS WAY
ON ORIGINAL

/S(S)/ APR 1 9 200

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: 12/ 28/ 1999	DUE DATE: 4/ 15/ 2000	OPDRA CONSULT #: 00-0007

TO:

Susan Allen, M.D.
Director, Division of Reproductive and Urologic Drug Products
(HFD-580)

THROUGH:

Jeanine Best
Project Manager
(HFD-580)

PRODUCT NAME: Cetrotide (Cetrorelix for Injection) **NDA #:** 21-197	**MANUFACTURER:** ASTA Medica Inc.

SAFETY EVALUATOR: Lauren Lee, Pharm.D.

OPDRA RECOMMENDATION:
OPDRA has no objections to the use of the proprietary name, Cetrotide. See the checked box below.

☑ FOR NDA/ANDA WITH ACTION DATE BEYOND 90 DAYS OF THIS REVIEW
This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from the signature date of this document. A re-review request of the name should be submitted via e-mail to "OPDRAREQUEST" with the NDA number, the proprietary name, and the goal date. OPDRA will respond back via e-mail with the final recommendation.

☐ FOR NDA/ANDA WITH ACTION DATE WITHIN 90 DAYS OF THIS REVIEW
OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from this date forward.

☐ FOR PRIORITY 6 MONTH REVIEWS
OPDRA will monitor this name until approximately 30 days before the approval of the NDA. The reviewing division need not submit a second consult for name review. OPDRA will notify the reviewing division of any changes in our recommendation of the name based upon the approvals of other proprietary names/NDA's from this date forward.

/S/ /for 4/18/00
Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

/S/ /for 4/19/00
Peter Honig, MD
Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B-03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE RECEIVED: December 28, 1999

NDA#: 21-197

NAME OF DRUG: Cetrotide (Cetrorelix for Injection)

NDA HOLDER: ASTA Medica, Inc.

I. INTRODUCTION:

This OPDRA consult is in response to a December 28, 1999 request by the Division of Reproductive and Urologic Drug Products, to review the proposed proprietary drug name, Cetrotide, regarding potential name confusion with other proprietary/generic drug names. Container label and container labeling were reviewed for possible interventions in minimizing medication errors.

PRODUCT INFORMATION

Cetrotide is a synthetic decapeptide with high and specific LHRH (luteinizing hormone releasing hormone) antagonistic activity and sequence homology to LHRH. Cetrorelix competes with natural LHRH for binding to membrane receptors on pituitary cells and thus controls the release of LH and FSH (follicle stimulating hormone) in a dose-dependent manner. Cetrotide is indicated for the prevention of premature ovulation in patients undergoing controlled ovarian stimulation. One regimen is to administer daily subcutaneous dose of Cetrotide 0.25 mg at the early to mid-follicular phase (Day 5 or 6 of stimulation) and is continued until and including the day of hCG administration. If the ovaries show an excessive response to the treatment with gonadotropins, continued administration of Cetrotide may be considered to prevent spontaneous ovulation and to reduce the risk of developing ovarian hyperstimulation syndrome (OHSS). Another regimen is to administer Cetrotide 3 mg subcutaneously on stimulation day 7. If hCG has not been administered within 4 days after injection of Cetrotide 3 mg, Cetrotide 0.25 mg should be administered once daily, beginning 96 hours after the injection of Cetrotide 3 mg until and including the day of hCG administration. Each pack of Cetrotide contains Cetrotide 0.25 mg in a 2 mL glass vial [or a 4 mL glass vial for Cetrotide 3 mg], a prefilled glass syringe with 1mL [or 3 mL] Sterile Water for Injection, one 20 gauge needle (yellow), one 27 gauge needle (grey), and two alcohol swabs.

II. RISK ASSESSMENT

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[1,2,3] as well as several FDA databases[4] for existing drug names which sound alike or

[1] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Emergindex, Reprodisk, Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).
[2] American Drug Index, online version, Facts and Comparisons, St. Louis, MO.

look alike Cetrotide to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[5]. An expert panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted prescription analysis studies consisting of an inpatient and an outpatient written prescription studies and a verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

[The expert panel consists of members of OPDRA's medication error Safety Evaluator Staff and a representative from the Division of Drug Marketing, Advertising and Communications (DDMAC)].

1. The panel discussed the following sound-alike/look-alike drug names:

Product Name	Generic name; strength	Usual Dose	Observation
Cetrotide	**Cetrorelix for injection**	**See Product Information above**	
Sandostatin	**Octreotide** acetate injection (0.05 mg/mL, 0.1 mg/mL, 0.2 mg/mL, 0.5 mg/mL, and 1 mg/mL	The initial dosage is usually 50 mcg administered twice or three times daily. Sandostatin may be administered subcutaneously or intravenously. Upward dose titration is frequently required.	*LA
Sandostatin LAR Depot	**Octreotide** acetate for injectable suspension (10 mg, 20 mg, and 30 mg)	Acromegaly- not currently receiving octreotide Begin with 50 mcg tid subcutaneously Acromegaly- currently receiving octreotide 20 mg given IM intragluteally at 4 week intervals for 3 months Carcinoid tumors- not currently receiving octreotide During the first 2 weeks of therapy, the daily dosage ranges from 100-600 mcg/ day in 2-4 divided doses. Carcinoid tumors- currently receiving octreotide 20 mg given IM intragluteally at 4 week intervals for 2 months. (See package insert for dosage adjustments)	*LA
Cetamide	Sulfacetamide sodium ointment (10 %)	A small amount (0.5 inch) into the lower conjunctival sac(s) 3 to 4 times daily and at bedtime.	*LA

*LA = Look-alike
*SA = Sound-alike

The panel identified octreotide and Cetamide but concluded that these names do not have the potential for name confusion with Cetrotide, and therefore, the proposed proprietary name is not objectionable. *Cetrotide is already available in the United Kingdom.*

2. DDMAC – no objections

[3] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[4] Drug Product Reference File [DPR], the Established Evaluation System [EES], the AMF Decision Support System [DSS], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, and the electronic online version of the FDA Orange Book.
[5] WWW location http://www.uspto.gov/tmdb/index.html.

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

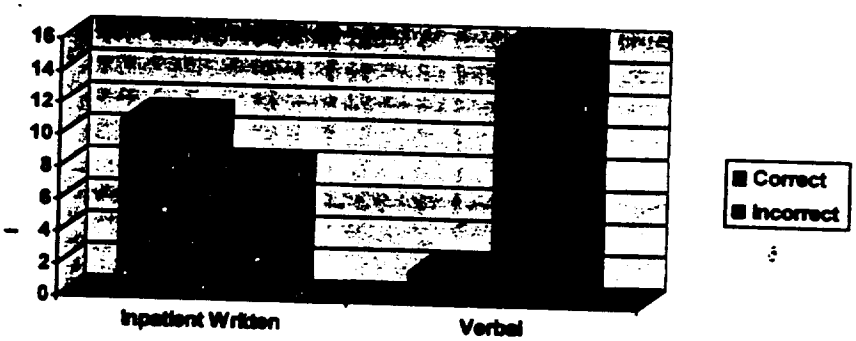
The studies conducted by OPDRA involved thirty-seven health professionals comprised of pharmacists, physicians, and nurses within FDA to determine the degree of confusion of Cetrotide with other drug names due to the similarity in handwriting and verbal pronunciation of the name. Written prescriptions, consisting of (known/unknown) drug products and a prescription for Cetrotide were scanned into a computer and were then delivered to a random sample of the participating health professionals via e-mail. In addition, verbal orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff. *(Outpatient written study was conducted with the proposed* [redacted] *instead of Cetrotide, and therefore, the results from this study were excluded in the review.)*

2. Results:

The results are summarized in Table I.

Table I

Study	# of Participants	# of Responses (%)	Correctly Interpreted	Incorrectly Interpreted
Inpatient Written	30	19 (63.3%)	11 (57.9 %)	8 (42.1 %)
Verbal	31	18 (58.1%)	2 (11.1 %)	16 (88.9 %)
Total	62	37 (59.7%)	13 (35.1 %)	24 (64.9 %)



C. SAFETY EVALUATOR RISK ASSESSMENT

1. A search in the Adverse Event Reporting System (AERS) was conducted to find any previously reported medication errors with Cetrotide. The AERS database was searched for reports using the Meddra term, DRUG MALADMINISTRATION, for Cetrotide% and Cetrorelix%. *There were no medication error reports located using this search.*

2. According to the expert panel discussion, Cetrotide was not considered to have the potential

for name confusion with existing product names and posed no significant safety risk. The panel identified octreotide and Cetamide but concluded that these names lack convincing verbal/written similarities to Cetrotide. In addition, the potential concerns regarding drug marketing and promotion related to the proposed name were also discussed and produced no objections by DDMAC.

According to the results of the verbal and written analysis studies, thirteen out of thirty-seven (35.1%) participants correctly interpreted Cetrotide. We recognize that low scores of correct interpretations would be common for all unapproved drug product names because health professionals are not familiar with the name. However, in this case, the majority of the respondents provided misspelled/phonetic variations of the drug name. In addition, the responses of the inpatient written and verbal studies did not overlap with any existing approved drug products. *(One participant from the outpatient written study, who incorrectly interpreted the name, further stated that the proposed name looks-alike octreotide. However, given the participant's interpretation and the proposed name used in this study, we cannot conclude that this participant actually confused Cetrotide and octreotide. [See methodology])* Therefore, there is insufficient evidence at this time to conclude that there is a safety risk of name confusion and to render the proposed proprietary name, Cetrotide, objectionable.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container label, carton and insert labeling of Cetrotide, OPDRA has attempted to focus on safety issues relating to possible medication errors. OPDRA has reviewed the current container label and carton and insert labeling and has identified several areas of possible improvement, which might minimize potential user error.

A. CONTAINER LABEL (0.25 mg & 3 mg)

1. We believe that the established name should be reflective of the way the product will be dosed in clinical practice. This would be consistent with current USP nomenclature practices. We recommend the following presentation for the established name:

Cetrotide
(Cetrorelix for Injection)

2. [redacted]

3. [redacted]

4. [redacted]

5. [redacted]

6. [redacted]

different colors, boxing, bolding etc.).

SYRINGE LABEL

1.

2.

B. **CARTON LABELING** (0.25 mg and 3 mg)

1.

2

C. **INSERT LABELING** (0.25 mg and 3 mg)

1.

2.

3.

IV. RECOMMENDATIONS:

A. OPDRA has no objections to the use of the proprietary name, Cetrotide.

B. OPDRA recommends the above labeling revisions that might lead to safer use of the product.

OPDRA would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Lauren Lee, Pharm.D. at 301-827-3243.

/S/ 4/18/00

Lauren Lee, Pharm.D.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

/S/ 4/18/00

Jerry Phillips, RPh
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

APPEARS THIS WAY
ON ORIGINAL

CC:

NDA: 21-197
Office Files
HFD-580; DivFiles; Jeanine Best, Project Manager
HFD-580; Susan Allen, Division Director
HFD-042, Mark Askine, Senior Regulatory Review Officer, DDMAC (Electronic Only)
HFD-400; Denise Toyer, Safety Evaluator, DDRE II, OPDRA
HFD-400; Jerry Phillips, Associate Director, OPDRA
HFD-400; Peter Honig, Director, OPDRA (Electronic Only)
HFD-002; Mac Lumpkin, Deputy Center Director for Review Management
(Electronic Only)

APPEARS THIS WAY
ON ORIGINAL

DEC C 6 19

REQUEST FOR PROPRIETARY/ESTABLISHED NAME REVIEW

To: Associate Director
Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
HFD-400

From: Suong Tran, Ph.D., Chemist 12/6/99
Division of Reproductive and Urologic Drug Products
HFD-580

Date: 06-DEC-1999

Application Status (IND/NDA/ANDA): NDA 21-197

Proposed Proprietary Name:
Cetrotide™ 0.25 mg and 3 mg (cetrorelix acetate for injection)

Trademark registration status/Countries registered(if known):
none

Company tradename:
ASTA Medica, Inc.

Other proprietary names by same firm for companion products:
none

United States Adopted Name, dosage form, strength and dosing schedule:
USAN: cetrorelix acetate
Dosage form: sterile powder to be reconstituted with sterile water for injection (SWFI)
Strength: 0.25 mg to be reconstituted in 1.0 mL SWFI or
3 mg to be reconstituted in 3.0 mL SWFI

Indications for use: Prevention of premature LH surges in women undergoing controlled ovarian stimulation.

Comments from submitter (concerns, observations, etc.):
PDUFA date: 29-OCT-2000
Desired date of OPDRA response: 29-APRIL-2000

APPEARS THIS WAY
ON ORIGINAL

Division Director Memorandum

AUG 0 8 2000

NDA#:	21-197
Sponsor:	Asta Medica, Inc.
Generic Name:	Cetrorelix Acetate for Injection
Proposed Trade Name:	Cetrotide™
Indication:	Inhibition of premature LH surges in women undergoing controlled ovarian stimulation
Dosage and formulation:	0.25 mg lyophilized powder for reconstitution with 1 ml of Sterile Water for Injection 3 mg lyophilized powder for reconstitution with 3 ml of Sterile Water for Injection
Regimen:	Multiple dose regimen (0.25 mg dose): Daily subcutaneous administration on cycle day 5 or 6 of controlled ovarian stimulation continued until and including the day of hCG administration Single dose regimen (3 mg dose): Single subcutaneous administration on the cycle day of controlled ovarian stimulation associated with an estradiol level indicative of an appropriate stimulation response as is typically seen on stimulation day 7. If hCG is not administered within 4 days of injection of 3 mg Cetrotide™, 0.25 mg should be administered daily by subcutaneous injection until and including the day of hCG administration.
Date of submission:	October 29, 1999
Date of memorandum:	August 8, 2000

Cetrorelix acetate (Cetrotide™) is a decapeptide analog of GnRH with antagonistic activity at the GnRH receptor. It is a new molecular entity and is the second GnRH-antagonist proposed for approval by the FDA for the indication of inhibition of LH surges in women undergoing controlled ovarian stimulation (COS) as a part of Assisted Reproductive Technology (ART) procedures. The sponsor seeks approval for two doses of Cetrotide™, a 0.25 mg dose for a multiple-dose regimen and a 3 mg dose for a single dose regimen.

The safety and efficacy of Cetrotide™ for the indication above was determined in five principle studies, two phase 2 dose-selection studies for the single and multiple dose regimens and three phase 3 studies as follows:

- Study 2997: Phase 2 study in which the 0.25 mg dose of Cetrotide™ was determined to be the lowest effective dose for the multiple-dose regimen
- Study 2986: Phase 2 study in which the 3 mg dose of Cetrotide™ was determined to be the lowest effective dose for the single-dose regimen
- Study 3010: Phase 3 open-label, active-controlled, safety and efficacy study of the 0.25 mg multiple-dose regimen of Cetrotide™ versus buserelin
- Study 3020: Phase 3 uncontrolled, supportive safety and efficacy study of the 0.25 mg multiple-dose regimen of Cetrotide™
- Study 3030: Phase 3 open-label, active-controlled, safety and efficacy study of the 3 mg single-dose regimen of Cetrotide™ versus triptorelin

Efficacy Results:

Efficacy for the desired indication was demonstrated in the three phase 3 studies, one of which (i.e., study 3020) provided supportive efficacy data. During early discussions with the sponsor about the design of the phase 3 studies, the primary endpoint for these trials proposed by the sponsor was the proportion of subjects reaching the treatment day of hCG administration. The Division agreed that this endpoint was acceptable but had to be accompanied and supported by data on pregnancy outcome. Because two of the three phase 3 studies used active controls that were not FDA-approved, the Division requested that the sponsor also compare the results from all phase 3 studies with those from historical data contained in the Society for Assisted Reproductive Technology (SART) registry database. Agreement was reached with the sponsor that efficacy assessments would also be based on the proportion of cycles with oocyte retrieval for the Cetrotide™-treated subjects, with comparison of that proportion to the number of cycles with oocyte retrieval out of all treatment cycles for a historical control (i.e., the SART registry database). The primary endpoint for the efficacy analyses in the phase 3 studies was reported as the proportion of subjects who failed to reach oocyte retrieval, resulting in cancellation of the treatment cycle (i.e., cancellation rate). It was agreed that an improvement of 10% in the cancellation rates for the Cetrotide™ treated patients as compared to historical controls would be clinically meaningful.

As described in detail in the primary and secondary clinical reviews, efficacy of both the single-dose and multiple-dose regimens were demonstrated in three phase 3 studies: Efficacy was demonstrated in terms of cycle cancellation rates (the primary efficacy endpoint), LH surge data, oocyte retrieval and pregnancy rates (secondary efficacy endpoints). These results are reported in the tables below:

Table 1: Efficacy Results:
Cancellation Rates for Single- and Multiple-Dose Cetrotide™ Regimens

Study #	Cetrotide™ - Dose	Treatment Regimen	Cancellation Rate: Cetrotide™	Cancellation Rate: Historical Control
3010	0.25 mg	Multiple dose	7.5%	22-28.5%*
3020	0.25 mg	Multiple dose	7.9%	22-28.5%*
3030	3 mg	Single dose	1.7%	22-28.5%*

*Rates determined from SART registry data and include cycles with and without the use of GnRH agonists

Table 2: Efficacy Results:
Pregnancy Rates per Attempt for Multiple- and Single-Dose Cetrotide™ Regimens

Study #	Cetrotide™ Dose	Treatment Regimen	Pregnancy rate: Cetrotide™	Pregnancy rate: Active Control	Pregnancy rate: Historical Control with GnRH Agonist Use
3010	0.25 mg	Multiple dose	20.7%	23.5%	23.7, 26.7%*
3020	0.25 mg	Multiple dose	19.8%	NA	23.7, 26.7%*
3030	3 mg	Single dose	22.6%	31%	23.7, 26.7%*

*Rates determined from 1995 and 1996 SART registry data and expressed as pregnancy rates per initiated cycle with GnRH agonist use

For several reasons, the primary statistical reviewer did not think the selected historical control group was appropriate for comparison of cancellation rates. Due to limitations in the design of study 3010 and 3020 as described in the primary and secondary clinical reviews, "administration of hCG" did not provide a clinically meaningful endpoint upon which treatment success could be measured. In addition, at the time of initiation and conduct of the phase 3 studies, no GnRH analogs (either agonists or antagonists) were approved in the U.S. for the ART indication. The Agency recommended and the sponsor agreed to compare the results from the clinical studies in the NDA to those of a historical control for the following reasons: (1) the lack of an approved GnRH analog for the ART indication at the time study 3010 and 3020 were conducted; (2) the use of unapproved active comparators in trials 3010 and 3020; and (3) concerns about the ethics of using placebo controls in ART trials.

As described in the clinical reviews, the National US In Vitro Fertilization-Embryo Transfer (IVF-ET) Registries published by SART are considered the best historical controls available for comparison. Although this database does not report LH surge data, cycle cancellation rates are reported by SART, and these rates (which are linked to oocyte retrieval) are thought to be more appropriate surrogate endpoints for the success of IVF than reaching the day of hCG administration.

For the reasons described above, and despite the limitations of the SART registry database, the primary endpoint chosen by the clinical reviewers (namely, treatment cycle cancellation rate) was appropriate and provided more clinically meaningful information than the originally proposed primary endpoint (i.e., reaching the day of hCG administration). In addition, data analyses for the phase 3 studies based upon cancellation rates were supported by pregnancy rate data and by analyses of other secondary efficacy parameters including inhibition of premature LH surges.

Safety Results:

Major safety issues of note in this application include ovarian hyperstimulation syndrome (OHSS), adverse fetal or neonatal outcomes, increases in hepatic transaminases, and injection site reactions. OHSS is the most serious safety concern in studies involving COS as a component of ART procedures. Moderate-to-severe OHSS occurred in 1.1%, 5.8% and 1.7% of the ITT Cetrotide™ treatment groups in studies 3010, 3020, and 3030, respectively. The higher incidence of OHSS for study 3020 was noted to be driven by one of the fourteen sites in that study (site #6). The results from this site were markedly different than those from other sites in the study, were not correlated to clinical findings or hormone levels and were therefore thought to be questionable. The overall rate of moderate-to-severe OHSS for the three phase 3 studies

combined (and including site #6 from study 3020) was 3.5%. This rate was noted to be higher than those reported previously for ART procedures but was not thought to be excessively high enough to impact the approvability of Cetrotide™.

In the Cetrotide™ treatment groups of the COS/ART studies described in the application, 3 of 223 newborns (1.3%) were noted to have a major congenital anomaly. This percentage is similar to the background rate of 2% of all newborns having a major congenital anomaly.

Of note, increases in hepatic enzymes (elevations 1.5 to 3 times the upper limit of normal) with no evidence of hyperbilirubinemia were noted in 2.6%, 2.3%, and 1.7% of Cetrotide™ treated subjects in the three phase 3 studies. The relationship of these enzyme elevations to Cetrotide™ administration is unknown. Elevation of hepatic transaminases has been associated with OHSS and these study findings could be related to controlled ovarian stimulation. Text related to this finding was incorporated into the label for Cetrotide™.

The most common adverse event in the phase 3 trials was injection site reactions which occurred in 9.6% and 1.7% of Cetrotide™-treated ITT subjects in studies 3010 and 3020, respectively, and in 25% of Cetrotide™-treated ITT subjects in study 3030. The higher rate of injection site reactions for study 3030 in which the 3 mg dose of Cetrotide™ was administered was thought to be due to the volume of injection for this dose (i.e., 3 ml) as compared to the volume for the 0.25 mg dose (i.e., 1 ml). All injection site reactions resolved within 24 hours of Cetrotide™ administration.

Conclusions and Recommendations:

I agree with the conclusions of the primary and secondary reviewers that the data contained in the NDA support the safety and efficacy of the 0.25 mg and 3 mg doses of Cetrotide™ for the indication of inhibition of premature LH surges in women undergoing controlled ovarian stimulation. I recommend approval of this application.

/S/ 8/8/00

Susan S. Allen, M.D., M.P.H.
Director, DRUDP, HFD-580

Cc: Division file NDA 21,197
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APPEARS THIS WAY
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Cetrotide™ Team Leader Review

NDA:	**21-197**
Drug:	**Cetrotide™ (Cetrorelix acetate for injection)**
Dosage Form/Route:	**In the multiple dose regimen-0.26-0.27 mg cetrorelix acetate (equivalent to 0.25 mg cetrorelix) sterile lyophilized powder to be reconstituted with 1 ml sterile Water for Injection in a pre-filled glass syringe. The dose is administered via subcutaneous injection once daily starting on cycle day 5 or 6 of controlled ovarian stimulation (COS) and continued either until and including the day of hCG administration (morning administration) or until the evening prior to the day of hCG administration (evening administration).** **In the single dose regimen-3.12-3.24 mg cetrorelix acetate (equivalent to 3.0 mg cetrorelix) sterile lyophilized powder to be reconstituted with 3 ml sterile Water for Injection in a pre-filled glass syringe. The dose is administered via subcutaneous injection as a single dose when the serum estradiol level is sufficient, usually stimulation day 7 (range days 5-12). If hCG is not administered within four day after injection of Cetrotide™ 3.0 mg, then Cetrotide™ 0.25 mg should be administered once daily beginning 96 hours after the injection of Cetrotide™ 3.0 mg until and including the day of hCG administration.**
Applicant:	**Asta Medica, Inc**
Original Submission Date:	**October 29, 1999**
Review Completed:	**July 27, 2000**
Date of Memorandum:	**July 28, 2000**

Background

Asta Medica is the second company to seek approval in this country of a GnRH antagonist for the prevention of premature luteinization in ART. The first GnRH antagonist, Antagon™ received approval from the Agency on July 29, 1999. Ten COS/Assisted Reproductive Technology (ART) studies (7 Phase 2 and 3 Phase 3) were submitted by Asta Medica to support this NDA application. Five are considered principle studies and are discussed in the Medical Officer's primary review. All 10 studies were conducted outside of the United States. Both a single dose and a multiple dose regimen program have been developed and submitted under the current NDA.

A guidance meeting between Asta Medica and the FDA was held in October of 1997. At that time Asta Medica stated that the three Phase 3 studies (two with GnRH agonists as active controls and one uncontrolled) would be submitted as adequate and well-controlled studies to support the

NDA. The Agency proposed that a historical control argument (including women who had undergone COS without the use of a GnRH agonist or GnRH antagonist) should be made for the use of cetrorelix in controlling premature LH surges, as the active comparators used in the studies (buserelin and triptorelin) were not approved in the U.S. Asta proposed analysis of the primary endpoint of "reaching the day of hCG" to provide evidence for efficacy of cetrorelix in the prevention of premature ovulation triggered by premature LH surges. The Agency agreed that this primary endpoint was acceptable provided that clinical data on pregnancy outcome was provided and supported the efficacy of the product. Asta was further informed that they should provide to the Agency further clarification on the use of the historical control data and reassurances on how secondary endpoints would be analyzed.

On September 29, 1998 a Teleconference was held to inform the Sponsor of the Agency's responses to the Sponsor's pre-NDA questions. These answers had been discussed in an internal meeting in preparation for the pre-NDA meeting with the Sponsor that was to take place on October 9, 1998. The Agency agreed that the historical control data provided by the Sponsor to the Agency, the National US In Vitro Fertilization –Embryo transfer (IVF-ET) Registries published (1985, 1986, 1988, 1989 and 1990) by the Society for Assisted Reproductive Technology (SART), were adequate for submission of the proposed NDA for cetrorelix. The Sponsor noted that it was not possible to compare "reaching the day of hCG" (the primary efficacy endpoint originally proposed for the Phase 3 studies) with the SART Registry, as these data were not reported. They proposed that the proportion of cycles (equal to the proportion of subjects for this one cycle treatment) with oocyte retrieval be compared to the number of cycles with oocyte retrieval in the historical control. This was acceptable to the Agency. The Sponsor proposed a 10% difference in success rates of patients undergoing oocyte retrieval between the historical control and cetrorelix treatment. The Agency found this to be acceptable. The Agency rejected the Sponsor's proposal to provide a one-sided 95% Confidence Interval of the difference. The Agency stated that either a two sided-95% Confidence Interval or a one-sided 97.5 % Confidence interval would be required. Non-clinical issues discussed included the chemistry requirements that impurity profile data should be submitted to ensure batch- to- batch consistency and stability data should be in accord with ICH Guidelines. The Sponsor and the Agency agreed that the Teleconference discussion was adequate and that a face-to-face meeting was not required.

A third pre-NDA meeting was held with the Sponsor on July 15, 1999. The objective of this meeting was to discuss deficiencies found at the Lübeck clinical trial site (Protocol 3020) and implications for the NDA to be submitted. It was agreed that the study report for 3020 could be done without data from the Lübeck site or it could be done both with and without this data. The data from the Lübeck site should not be included in the efficacy analysis for cetrorelix. The Lübeck safety data could be retained in the ISS.

NDA 21-197 for Cetrotide™ was received by the Agency on October 29, 2000.

Chemistry/ Manufacturing

The following summary addresses the major issues identified in the chemistry review.

Cetrorelix acetate is a decapeptide analog of GnRH in acetate which has antagonistic activity at the GnRH receptor. It is a new molecular entity and has ten chiral centers including five non-natural amino acids.

The drug substance is jointly manufactured by [redacted] which manufactures

[redacted]. Both manufacturing facilities comply with cGMP. The structure of the peptide as characterized by multiple techniques was assessed to be correct. The proposed specifications and analytical methods to assess quality control were considered to be satisfactory. Based on the available stability data, a retest period of 12 months is established when stored at 2-8°C.

Asta Medica AG, Germany, manufactures the drug product, and [redacted] These facilities are both in compliance with cGMP. The specifications for assay methods and impurities for release and shelf life were established separately and are considered satisfactory.

Three pilot scale batches of each of the 0.25 mg and 3.0 dosage strengths were subjected to stability studies under ICH conditions up to 24 months. [redacted] manufactured these batches and they all met the shelf-life specifications. However, when commercial scale batches were produced with the drug substance manufactured by [redacted], the 0.25-mg strength showed lower stability when compared to the pilot batches. The Sponsor accepted a 24-month expiry date at 2-8°C for the 0.25-mg dosage strength and a 24-month expiry at 25 ° for the 3.0-mg dosage strength.

The Sponsor's responses to deficiencies noted in the microbiology review were considered satisfactory.

The NDA is considered acceptable for approval from a Chemistry, Manufacturing and Controls point of view.

Product Name

The Sponsor submitted an application on May 17, 2000 to the USAN council for the established name "cetrorelix acetate" and this was accepted on June 28, 2000.

The tradename, Cetrotide, was recommended by OPDRA for acceptance on April 19, 2000.

Pre-clinical Pharmacology and Toxicology

The following is a summary of findings from the pre-clinical pharmacology and toxicology review.

In the toxicity studies in rats and dogs, pharmacodynamic effects of treatment were seen but very little systemic toxicity was observed. At the injection site, treatment-related changes consisted of macrophage infiltrates, focal fibrosis, focal edema and focal necrosis. These changes showed a dose-related increase in incidence and severity.

In both the 4-week and 13-week rat toxicity studies the low dose of cetrorelix increased in an agonistic fashion, testosterone in the male and estradiol in the female. Hepatic enzymes were increased in both studies. In the 26-week rat toxicity study, there was atrophy of the adrenal gland zona reticularis in all treated groups. Bone density was decreased in both the 13-and 26-week toxicity studies. Bone density changes were not seen in treated dogs.

In the maximum tolerated dose-finding studies in rats, an agranuloma-like reaction occurred at the injections site and subsequent injections of cetrorelix into the vascularized granuloma tissue led to a quasi-intravenous reaction with mast cell degranulation, clinical symptoms of

hypotensive shock and death. A study of intravenous injections in 12 human subject produced no such adverse events. Nevertheless, the reviewer suggests that care should be taken to avoid accidental intravenous administration. The label (Administration Section) will adequately address this point.

Cetrorelix was not mutagenic in *in vitro* testing (Ames test, HPRT test, chromosome aberration test) or *in vivo* testing (chromosome aberration test, mouse micronucleus test) testing. Cetrorelix induced polyploidy in CHL-Chinese hamster lung fibroblasts, but not in V79-Chinese hamster lung fibroblasts, cultured peripheral human lymphocytes or in an *in-vitro* micronucleus test in the CHL-cell line. The significance of polyploidy in humans is unknown. Long-term carcinogenicity studies in animals have not been performed with cetrorelix

Treatment with 0.46mg/kg cetrorelix for 4 weeks resulted in complete infertility in female rats, which was reversed 8 weeks after cessation of treatment.

When administered to rats for the first seven days of pregnancy, cetrorelix did not affect the development of the implanted conceptus at doses up to 38 µg/kg (approximately 1 times the recommended human therapeutic dose based on body surface area). However, a dose of 139 µg/kg (approximately 4 times the human dose) resulted in resorption rate and post-implantation loss of 100%. When administered from day 6 to near term to pregnant rats and rabbits, very early resorptions and total implantation losses were seen in the rat at doses from 4.6µg/kg (0.2 times the human dose) and in the rabbit at doses from 6.8 µg/kg (0.4 times the human dose). In animals that maintained their pregnancy, there was no increase in the incidence of fetal abnormalities.

The pre-clinical safety evaluation suggests that cetrorelix is safe for the short-term use as an adjunct therapy to controlled ovarian stimulation. From a Pharmacology (pre-clinical) point of view the NDA is acceptable for approval.

Biopharmaceutics

The pharmacokinetics and bioavailability of cetrorelix was addressed in 20 studies submitted to the NDA. The following observations and conclusions were made upon review of these studies.

Cetrorelix is well absorbed from subcutaneous administration, with T_{max} of 1-2 hours. Cetrorelix shows linear and dose proportional pharmacokinetics in females (and males) after single and multiple dose administration of 1mg/ml. The absolute bioavailability is approximately 85%. The $T_{1/2}$ of cetrorelix following subcutaneous administration is approximately 50 – 100 hours. The volume of distribution following intravenous administration was approximately 1 L/Kg. The metabolism of cetrorelix was not investigated in humans. After subcutaneous administration of 10 mg of cetrorelix, unchanged drug and small amounts of derived peptides were found in the bile samples over 24 hours. Cetrorelix is transformed by peptidases and the amino acid 1-4 peptide is the predominant metabolite. Because Cetrorelix is a peptide, it is expected that it will be metabolized by peptidases prior to presentation to the liver. It is expected that cytochrome P450 enzymes do not metabolize Cetrorelix and, therefore, no specific drug interaction studies were conducted and this was acceptable to the Biopharmaceutics reviewing team. Population PK analysis was not required as the indication is for use only in young healthy females.

From a Biopharmaceutics perspective, the NDA is acceptable for approval.

Division of Scientific Investigations (DSI)-Clinical Inspection Summary

In addition to the Lübeck site that was excluded by both the Sponsor and the FDA, there was a second site of concern. The evaluative report of the clinical inspections for NDA 21-197 noted that clinical site #24 (Glasgow) in study 3020 had some deficiencies (noted by the principle investigator and conveyed to the FDA). The Sponsor was unable to provide the original ultrasound data to document ultrasound evaluations in the study. Therefore, DSI was unable to assess and verify the study data from the Glasgow site. The recommendation from the DSI reviewer was that data from this clinical site not be used in the efficacy analysis. The Medical Officer accepted this recommendation and excluded the Glasgow site from his analysis of efficacy. The safety information from this site was considered. Inspections were conducted at the Copenhagen, DK and Edinburgh, UK sites for Study 3010 and the Clamart, FR site for Study 3030. These sites were all acceptable.

Clinical Efficacy and Safety

Dose selection studies

Study 2997 (multiple dose regimen)

Study 2997 was a Phase II open-label, dose-finding study conducted in one center and designed to select for the multiple dose regimen, the minimal effective dose of cetrorelix in preventing premature surges of endogenous LH in women undergoing COS with human menopausal gonadotropin (hMG). Previous proof of concept studies had identified the 0.5-mg dose of cetrorelix utilized in the multiple dose regimen as being effective in the suppression of the LH surge. In Study 2997, subjects were started on the 0.5-mg dose. The protocol allowed for the treatment dose to be titrated up if a LH surge occurred in the 0.5-mg treatment dose or down (0.25 mg, 0.1 mg) if 30 subjects were treated in a dosing arm without the occurrence of a LH surge. The cetrorelix dose was administered once daily subcutaneously into the abdominal wall starting on cycle day 6 of hMG therapy and continuing up to and including the day of hCG. The dose of hMG could be adjusted depending on the individual ovarian response as assessed by serum estradiol level. Human chorionic gonadotropin (hCG), 10,000 IU, was administered when three follicles with a mean of 17 mm was observed by ultrasound. Oocyte retrieval was performed 36h later. Fertilization was established by IVF with or without intracytoplasmic sperm injection (ICSI). Embryo transfer was performed with a maximum of three embryos replaced. The protocol was amended to allow subjects to receive luteal phase support in the form of progesterone or hCG. The first six subjects received no luteal phase support. In the event of a premature LH rise (LH > 10 IU/L and progesterone > 1 ng/ml), the investigator was allowed to either cancel or rescue the cycle by giving hCG, even though the criteria for hCG administration had not been reached.

Of the 90 subjects who received cetrorelix, 32 subjects received the 0.5 mg dose, 50 subjects received the 0.25 mg dose (4 of these 50 patients also received the initial treatment at the 0.1 mg dosage) and 8 subjects received the 0.1 mg dose. One subject on the 0.1-mg dose of cetrorelix experienced a LH surge (LH > 10 IU/L and progesterone > 1 ng/ml). No subject on the 0.5-mg or 0.25 dose of cetrorelix experienced a LH surge. There were no cycle cancellations on the 0.25-mg dose. The 0.25-mg dose of cetrorelix was selected as the minimally effective dose in the multiple dose regimen. Twenty-five (25) pregnancies occurred (rate=28%/cycle). Eleven of these pregnancies were in the 0.25 mg selected dose. The pregnancy rate of the 0.25 mg selected dose (22%) compared favorably with the historical control rate (8-10%/cycle for those years prior to GnRH agonist therapy).

No subjects discontinued the study because of an adverse event. There were 6 cases of OHSS reported including one associated with severe right renal colic. These subjects all required hospitalization. The cases occurred in both the 0.5-mg (4) and the 0.25-mg dose (2). Four of the six cases were associated with pregnancy (moderate to severe cases of OHSS occur more frequently with pregnancy). The conclusion drawn upon review of the individual cases of OHSS is that the higher than usual rate of OHSS in this study as opposed to that usually seen in assisted conception cycles [0.1 –2.0%]) was most likely due to the liberal administration of hCG in individuals with a high number of follicles≥15 and high estradiol levels.

Local redness at the injection site was found in 51% of the patients, redness and itching in 30%, redness and swelling in 6%. These were resolved within 24 hours and felt not to be a major tolerability issue. Hepatic enzyme changes were reported in four subjects. The rate of enzyme elevations after exclusion of one patient with a pre-existing condition was 3.3% (3/90). No elevation of bilirubin was observed.

There was one twin pregnancy in which the male infant was later diagnosed with a VSD and the female was noted to have minor motor delay. In addition there was a fetal death in utero at 24 weeks of gestation. No congenital anomalies were noted in this fetus.

The 0.25-mg dose was determined to be the minimal effective dose in the multiple dose regimen and it was shown to be safe and tolerated. The selection of this dose appears to be valid and appropriate.

Study 2986 (single dose regimen)

Study 2986 was a Phase 2 open-label, dose-finding study conducted in two centers and designed to select for the single dose regimen, the minimal effective dose of cetrorelix in preventing premature surges of endogenous LH in women undergoing COS with human menopausal gonadotropin. Previous proof of concept studies had identified the 5.0-mg dose of cetrorelix utilized in a single dose regimen as being effective in the suppression of the LH surge. In study 2986, initially subjects were treated with 3.0-mg cetrorelix. The protocol allowed for the treatment dose to be titrated up (e.g. 3.0 mg to 5.0 mg) if a LH surge occurred in the treatment dose or down (2.0 mg, 1.0 mg or 0.5 mg) if 30 subjects were treated in a dosing arm without the occurrence of a LH surge. The cetrorelix dose was administered once subcutaneously into the abdominal wall on cycle day 7 of hMG therapy. The dose of hMG could be adjusted depending on the individual ovarian response as assessed by serum estradiol level. Human chorionic gonadotropin (hCG), 10,000 IU, was administered when the lead follicles were 18 –20 mm as observed by ultrasound and the serum estradiol was greater than 250 pg/ml per follicle. Oocyte retrieval was performed 36h later. Fertilization was established by IVF with or without intracytoplasmic sperm injection (ICSI). Embryo transfer was performed with a maximum of three embryos replaced. All subjects received luteal phase support in the form of progesterone (intramuscular or intravaginal) or hCG. In the case of a premature LH rise (LH > 10 U/L following several antecedent rising levels of LH), the investigator was allowed to either cancel or rescue the cycle by giving hCG, even though the criteria for hCG administration had not been reached.

Thirty (30) subjects were started on 3.0-mg cetrorelix, the next 31 patients were treated with 2-mg cetrorelix and the final 3 subjects were treated with 3.0-mg cetrorelix. One subject on the 2.0-mg dose of cetrorelix experienced a LH surge (defined in this protocol as LH > 10 U/L

following several antecedent rising levels of LH). No subject on the 3.0-mg dose of cetrorelix experienced a LH surge. There were no cycle cancellations. The 3.0-mg dose of cetrorelix was selected as the minimally effective dose in the single dose regimen. Nineteen clinical pregnancies (rate=29%/cycle) were reported. Eleven of these pregnancies were in the 3.0 mg selected dose. The 33%/cycle pregnancy rate (11/33) on the 3.0 mg selected dose compared favorably with the historical control rate (8-10%/cycle for those years prior to GnRH agonist therapy).

No subjects discontinued the study because of an adverse event. A total of 29 subjects experienced at least one adverse event. This is not an unusually high number. No serious adverse events occurred. No cases of ovarian hyperstimulation syndrome (OHSS) were reported. Injection site reaction occurred in 44% (28/64) of subjects on cetrorelix. The reaction resolved by 24 hours post-injection. No congenital anomalies were reported in the infants conceived during this study. No abnormal development problems were noted during subsequent follow-up of the children which was at least one year.

The 3.0-mg dose was determined to be the minimal effective dose in the single dose regimen. It was associated with a favorable pregnancy outcome and was shown to be safe and tolerated. The selection of this dose appears to be valid and appropriate.

Phase 3 Clinical Trials

Study 3010 (multiple dose regimen)

Study 3010 was the pivotal study to demonstrate the efficacy and safety of cetrorelix 0.25 mg in a multiple dose regimen in women undergoing controlled ovarian hyperstimulation. It was a Phase 3, multi-center, open-label, randomized study using buserelin as a reference treatment. The randomization of subjects to treatment was 2:1 cetrorelix to buserelin. A total of 188 subjects were randomized to 0.25mg cetrorelix and 86 subjects to the buserelin group. The protocol allowed for the replacement of subjects who had been randomized but who did not return for visit 1. The study was designed as a non-inferiority study.

Subjects in the cetrorelix treatment group received hMG (150 IU) by intramuscular injection once daily starting on the 2nd menstrual cycle day. Individualization of the hMG dose according to individual ovarian response was allowed after cycle day 5. Cetrorelix (0.25mg), administered by subcutaneous injection once daily (morning) into the lower abdominal wall, was started on day 6 of hMG treatment. Treatment with hMG and cetrorelix was continued up to and including the day of hCG administration.

Subjects in the buserelin group began treatment between cycle day 18 and 22 of the previous menstrual cycle after a hCG test was performed to exclude pregnancy. Buserelin was administered intranasally with one puff (0.15 mg) given four times per day. HMG was begun when a down-regulated hypogonadotropic state (defined as estradiol < 50pg/ml) was reached. If hormonal suppression were not obtained or if an ovarian cyst was present, buserelin treatment was continued for 1 additional week prior to the start of hMG. Any subject, who had not achieved down regulation within 15 days of treatment, had treatment discontinued. Individualization of the hMG dose according to individual ovarian response was allowed after cycle day 5. Buserelin and hMG were continued up to and including the day of hCG administration.

For both treatment groups hCG (10,000 IU) was administered on the day of treatment in which at least 1 follicle ≥ 20 mm was measured by ultrasound or the estradiol level was ≥ 1200 pg/ml. HCG was not administered when there were 12 or more follicles with a mean diameter ≥15-mm or an estradiol level ≥ 4000 pg/ml. A premature LH surge (LH≥10 IU/l and serum progesterone≥1 ng/ml) occurring before or on the day of cetrorelix or buserelin administration would result in cycle cancellation. In addition, the cycle was to be cancelled for low estradiol (<1200 pg/ml), insufficient follicular development (according to the above criterion), poor tolerability of the drug, intercurrent disease, violations of the exclusion criteria, or non-compliance. However, the investigator was given the discretion of "rescuing the cycle" (administer the hCG and proceed on to oocyte retrieval) if the LH surge occurred during the hMG stimulation phase.

Oocyte retrieval was performed 36 hours after hCG administration. IVF with or without ICSI was performed and embryo transfer was done 2 days after oocyte retrieval. Embryo transfer was limited to replacement of a maximum of 3 embryos. Luteal phase support with progesterone was given according to the investigator's routine practice. Each subject was treated for only one IVF cycle.

The primary efficacy endpoint was the proportion of subjects reaching the day of hCG. This endpoint was originally accepted by the Agency provided the pregnancy rate was supportive of efficacy. However, as indicated above, subjects who had a LH surge unaccompanied by poor follicular development or low estradiol levels were allowed to receive hCG per protocol. This makes reaching the day of hCG an endpoint from which no meaningful conclusions could be drawn. Prior to the submission of the NDA, the Agency and the Sponsor agreed to base the efficacy analysis on the proportion of subjects with oocyte retrieval and to compare that to a historical control. Therefore, a cycle cancellation rate was determined based on the number of subjects who failed to have oocyte retrieval. This was the efficacy analysis considered by the reviewing medical officer. The Sponsor reported that 10 subjects failed to have oocyte retrieval (178 subject had oocyte retrieval) out of the 188 Intent-to-Treat cetrorelix subjects. This yielded a cancellation rate of 5.3%. In the Medical Officer's efficacy analysis, subjects who had an LH surge, but who were given hCG any way were excluded from the number of subjects reaching oocyte retrieval and were treated as failures. The Medical Officer's efficacy analysis also excludes the Glasgow Scotland site (see under DSI section) which had 29 subjects on cetrorelix. The Medical Officer's analysis yielded a cycle cancellation rate of 7.5% (12/159). I agree with the Medical Officer's analysis of the cycle cancellation rate. Both the cycle cancellation rate of 5.3% as calculated by the Sponsor and the rate of 7.5% as determined by the medical officer are greater than a 10% improvement over historical rates (28.5% including cycles with and without the use of GnRH agonists)

Forty-Five (45) pregnancies occurred in subjects treated with cetrorelix 0.25mg in this study. Forty-two (42) of these occurred during the treatment cycle and three resulted from cryopreservation cycles. The pregnancy rate of 22.3 % per attempt compares favorably with the historical control rate of 4.7 – 18.1 % (SART pregnancy rate per cycle data for 1985, 1986, 1988, 1989, and 1990). The pregnancy rate excluding Glasgow is 20.7%/cycle. This rate compares favorably to the historical control data presented by the Sponsor (8-10%/cycle in 1985 and 1986 prior to the use of GnRH agonists) and is consistent with the rates of 23.7% and 26.7 % per initiated cycle, from the 1995 and 1996 SART registries (with GnRH agonists use). The take home baby (includes multiple gestation) rate of 16%/cycle compares well to that of the historical control (11%/cycle for 1985 and 1986). There were 8 sets of twins.

Secondary efficacy parameters analyzed for efficacy include pregnancy rates and LH surge data discussed above and oocyte retrieval data. These secondary efficacy parameters were all acceptable and supportive of the efficacy of the 0.25 dose.

The safety profile of the 0.25-mg dose of cetrorelix in the multiple dose regimen was acceptable. There were no deaths reported. The only serious subject adverse event reported was OHSS. Moderate to severe (WHO classification II-III) OHSS, occurred in 1.1% of the ITT group on cetrorelix compared to 5.8% of the ITT group on buserelin. The most common adverse events on cetrorelix treatment were injection site reaction, occurring in 9.6% of ITT subjects and headache, occurring in 2.1% of ITT subjects. Changes in hepatic enzymes were noted in 4.7% of subjects treated with cetrorelix and 3.4% of buserelin treated subjects. Correction of the data for preexisting enzyme elevation or other conditions associated with enzyme elevations resulted in a rate of 2.6% hepatic enzyme elevations on cetrorelix vs1.1% with buserelin. There was no increase in bilirubin in any of these subjects.

Evaluation of the pregnancy and newborn adverse events revealed that there was one stillbirth, one case of intrauterine growth retardation diagnosed at 34 weeks gestation and one infant from a twin pregnancy with anencephaly.

Study 3020 (multiple dose regimen)

Study 3020 is considered a supportive study for the efficacy of the 0.25-mg dose of cetrorelix in the multiple dose regimen. The study was considered supportive because it was an uncontrolled study. The trial design and conduct was very similar to 3010 (with the exception of no control). A total of 346 subjects were treated with cetrorelix. After an internal audit revealed data management problems at the Lübeck clinical (which accounted for 43 subjects), data from this site was excluded from the efficacy analysis, but not the safety analysis. The Agency agreed with this decision (see background discussion).

The Sponsor calculated a cycle cancellation rate of 6.9% (Lübeck excluded). The medical officer's review revealed a rate of 7.9%. These rates are both greater than a 10% improvement over the historical rate (28.5%) and support the efficacy of the 0.25-mg dose of cetrorelix in the multiple dose regimen. LH surge data (2%) and pregnancy data also support the efficacy. Sixty subjects out of 303 subjects treated with 0.25 mg of cetrorelix became pregnant. The pregnancy rate of 19.8% compares favorably with the historical controls (8. – 10% prior to the use of GnRH agonists). The live birth rate was 25.4%. There were 16 sets of twins and one set of triplets.

There were no deaths in this study. Twenty cases (5.7% of ITT) of moderate to severe OHSS occurred. One clinical center (site 6) seemed to be driving this higher rate of OHSS. No other serious adverse events were reported. There were 6 cases (1.7%) of injection site reaction, 3 cases of nausea and 3 cases of headache. When OHSS and preexisting elevations are excluded, hepatic enzyme elevations were reported in 2.3% of subjects.

There was one adverse fetal/neonatal outcome, a stillbirth. In addition, there was one set of twins both with Q-T syndrome (prolongation of the QT interval). No further significant adverse outcomes in babies were noted in the four-month safety update of the study.

Study 3030 (single dose regimen)

Study 3030 was the pivotal study to demonstrate the efficacy and safety of cetrorelix 3.0 mg in a single dose regimen in women undergoing controlled ovarian hyperstimulation. It was a Phase 3 multi-center, open-label, randomized study using triptorelin as a reference treatment. The randomization of subjects to treatment was 3:1 cetrorelix to triptorelin. A total of 115 subjects were randomized to 3.0-mg cetrorelix and 36 subjects to the triptorelin group. The protocol allowed for the replacement of subjects who had been randomized but who did not return for visit 1. The study was designed as a non-inferiority study.

Subjects in the cetrorelix treatment group received hMG (150 IU) by intramuscular injection once daily starting on day 2 of the menstrual cycle. Individualization of the hMG dose according to individual ovarian response was allowed after cycle day 4. Cetrorelix (3.0 mg) was administered by subcutaneous injection on day 7 of hMG treatment or when the serum estradiol level was greater than 400pg/ml. If the subject did not meet the criteria to receive hCG within 4 days after the 3.0 mg injection of cetrorelix, daily subcutaneous injections of 0.25 mg cetrorelix were done from the 5th day after the 3.0 mg dose (hMG day 12) onward until the day that hCG was given.

Triptorelin was administered as a single 3.75-mg intramuscular dose between menstrual cycle day 18 and 22 (midluteal phase) of the previous cycle. Individualization of the hMG dose according to individual ovarian response was allowed after day 4 of hMG treatment.

For both treatment groups, hCG (10,000 IU) was administered on the day of treatment in which at least 1 follicle≥ 18 mm was measured by ultrasound or the estradiol level was ≥ 1,200 pg/ml. HCG was not administered when there were 12 or more follicles with a mean diameter ≥15 mm or an estradiol level ≥ 4000 pg/ml. A premature LH surge (LH≥10 IU/l and serum progesterone≥1 ng/ml) occurring before or on the day of cetrorelix or triptorelin administration would result in cycle cancellation. In addition, the cycle was to be cancelled for low estradiol (<1200pg/ml), insufficient follicular development (according to the above criterion), poor tolerability of the drug, intercurrent disease, violations of the exclusion criteria, or non-compliance. However, the investigator was given the discretion of "rescuing the cycle" (administer the hCG and proceed on to oocyte retrieval) if the LH surge occurred during the hMG stimulation phase.

Oocyte retrieval was performed 36 hours after hCG administration. IVF with or without ICSI was performed and embryo transfer was done 2 days after oocyte retrieval. Embryo transfer was limited to replacement of a maximum of 3 embryos. Luteal phase support with progesterone was given according to the investigator's routine practice. Each subject was treated for only one IVF cycle.

The primary efficacy endpoint was absence of a LH surge as defined by a LH level ≥ 10 IU and progesterone level ≥ 1ng/ml. There were no LH surges after dosing of cetrorelix in the 115 subjects who received the 3.0-mg cetrorelix dose. Of the 115 subjects, eleven subjects received one or two additional doses of 0.25-mg cetrorelix. The secondary efficacy parameters of cycle cancellation rate (1.7%), and pregnancy rate (23%) were both supportive of the efficacy.

The safety profile of the 3.0-mg dose of cetrorelix in the single dose regimen was acceptable. There were no deaths reported. Moderate to severe OHSS occurred in 1.7% (2/115) of the ITT

group on cetrorelix compared to 2.5% (1/39) of the ITT group on triptorelin. One other serious adverse event occurred in the 3.0-mg cetrorelix group, an abdominal infection following oocyte retrieval which was considered secondary to the retrieval. The most common adverse event on cetrorelix treatment was injection site reaction, occurring in 25% of ITT subjects. These site reactions were resolved within 24 hours. When OHSS and preexisting elevations were excluded, hepatic enzyme elevations were reported in 1.7% of subjects.

There were no stillbirths or neonatal adverse events.

Historical Control

The historical control presented by the Sponsor in support of this application was the National US In Vitro Fertilization –Embryo transfer (IVF-ET) Registries published by SART for the years 1985, 1986, 1988, 1989 and 1990. The Agency agreed to this historical control. The SART data prior to 1989 reflect IVF results prior to the widespread off label use of GnRH agonists (to reduce the incidence of premature LH surge) in controlled ovarian stimulation protocols. In 1988, 43 % of IVF clinics reported administering GnRH agonists. The use of GnRH agonists among clinics reporting to SART increased to 73% in 1989 and 97% in 1990. The use of GNRH agonists has remained at this level or above since. The SART data presented by the Sponsor gives a cycle cancellation rate of 28.5 for the combined years 1985-86 with 1988-90. This figure does not purely reflect IVF results prior to GnRH agonists as these agents were used with increasing frequency beginning in 1989

Discussion and Conclusions:

Efficacy

The Sponsor originally proposed to the Agency the primary endpoint of reaching the day of hCG as supporting the efficacy of cetrorelix in the prevention of premature LH surges. While the administration of hCG to trigger final follicular maturation is one measure of success of the controlled ovarian stimulation protocol, it does not reflect whether the product was successful in inhibiting a LH surge (particularly if investigators were allowed to give hCG even if a LH surge had occurred or was in progress). Reaching the day of hCG is also not a good surrogate for success of IVF. The presentation of LH surge data would have been the most objective and direct primary endpoint (this was retained as the primary endpoint for study 3030). However, it was necessary to compare the results from the clinical studies presented in this NDA to a historical control, as the active comparators utilized are not approved in this country. Of course, the use of a placebo control (i.e. gonadotropins alone without GnRH antagonists or agonists) would have allowed for the most unambiguous interpretation. However, at the time of the conduct of these trials in 1995, this and several other Sponsors had successfully argued to the Agency that the use of GnRH agonists in COS/ART was "standard of care" and to offer placebo treatment to these patients would be "unethical". The best available historical controls are the National US In Vitro Fertilization –Embryo transfer (IVF-ET) Registries published by SART. However, the SART registries do not report LH surge data. The Sponsor revised the primary endpoint to the proportion of subjects with oocyte retrieval and calculated a cycle cancellation rate (percent who failed to have retrieval) which is a parameter reported by SART. Oocyte retrieval is a better surrogate endpoint for the success of IVF or IVF/ ICSI. Studies 3010 and 3020 have the proportion of subjects to reach retrieval and the calculated cycle cancellation rates as the primary endpoint. Clinical pregnancy resulting in live birth is the ultimate measure of the success of IVF programs. The clinical pregnancy rates were determined in this application as secondary parameters.

SART IVF Registry data clearly support that in controlled ovarian stimulation protocols for IVF, GnRH agonist therapy has improved the cancellation rates (failure to reach oocyte retrieval) from 25% to 30 % prior to GnRH down to 14 % (1995 and 1996 SART registry data published in 1998 and 1999,respectively). Although the SART registry does not record LH surge data, it has been shown that the majority of cycle cancellations prior to widespread use of GnRH agonists were for premature luteinization resulting in immature and poor quality oocytes. Undoubtedly there are other factors that may have contributed to this improvement in cancellation rates. However, the use of GnRH agonists appears to be the driving force. The published SART IVF Registry data would suggest a more modest increase in pregnancy rates ranging from 10% to 60% with the use of GnRH agonists.

The dose selection (lowest effective dose) of the 3.0-mg dose of cetrorelix for the single dose regimen was based on Study 2986 in which there were no LH surges in subjects treated with this dose. The efficacy of this dose was established in Study 3030. There were no LH surges in subjects treated with the 3.0-mg dose. The cycle cancellation rate of 1.7% is not only greater than 10% better than the historical data presented in the applications (28.5%) but is substantially better than the cycle cancellation rate of 14% reported in the most recent SART Registry data (1995 and 1996 which reports on cycles with ≥ 97% GnRH agonist use). The pregnancy rate of 23% compares favorably to the 8-10% pregnancy rate reported in the 1985 – 1986 SART registries (prior to the use of GnRH agonists) and is consistent with the 24- 27%/cycle rate reported in 1995 and 1996 SART registries. The "take home baby" rate of 23%/cycle also compares well.

The dose selection (lowest effective dose) of the 0.25-mg dose of cetrorelix for the multiple dose regimen was based on study 2997 in which there were no LH surges in subjects treated with this dose. The efficacy of this dose was established in Studies 3010 and 3020. The cycle cancellation rate of 7.5% in the controlled Study 3010 and 7.9% in the uncontrolled Study 3020 are greater than 10% better than the historical data presented in the applications (28.5%). The Sponsor's and the Medical Officer's rates are also both better than the cycle cancellation rate of 14% reported in the most recent SART Registry data (1995 and 1996). The pregnancy rate of 20% compares favorably to the 8-10% pregnancy rate reported in the 1985 – 1986 SART registry data (prior to the use of GnRH agonists) and is consistent with the 24- 27%/cycle rate reported in 1995 and 1996 SART registries. The live birth rate from the combined studies, 22%/cycle, also compares well.

Safety

The major safety issues to address in a study utilizing controlled ovarian stimulation regimens for ovulation induction or ART are the risk for OHSS, multiple gestation and adverse fetal/neonatal outcomes. As GnRH antagonists are utilized as adjunctive therapy in such regimens, these issues are also important to address in studies of these agents. Indeed, some published reports have suggested that, compared to the risk with gonadotropin stimulation alone, the risk of OHSS may be higher in subjects receiving controlled ovarian stimulation with adjunctive GnRH agonist therapy. Whether the same will be true with GnRH antagonists remains to be established. The rates of moderate to severe OHSS in Studies 3010, 3020 and 3030 range from 1.7 –5.7%. The higher rate occurred in the noncontrolled Study 3020 and was driven by study site 6 which had a disproportionally high rate of total OHSS with some cases having no correlation between the diagnosis of moderate to severe OHSS and elevated estradiol levels. If data from this site were not considered in the percentage of moderate to severe OHSS, then the rate of moderate to severe OHSS in the Phase 3 trials would be 2.0%, a rate which is more in-line with the 0.1-2% rate of OHSS reported in ART. In the 949 subjects considered in the safety base of the 10 controlled ovarian stimulation/ART trials submitted with the NDA, the rate of moderate to severe OHSS

was 3.5 % (33/949, driven mostly by site 6, Study 3020) which is higher than rates of moderate to severe OHSS reported in ART. The clinical review team does not consider the 3.8% rate of OHSS to be an approvability issue because the rate is not excessively high and it was clearly driven by a single center. Further, GnRH antagonists are not the primary cause of OHSS, which is caused by overstimulation with gonadotropins and the actual rates of OHSS seen in the comparative trials were lower in the cetrorelix arms than in the GnRH comparator arm. These trials were not powered to assess the significance of this difference. The rate of OHSS in the ITT safety base will be included in the Adverse Reactions section of the label.

Injection site reaction was a common occurrence in subjects treated with the 3.0-mg dose occurring in 25% of the ITT population in the Phase 3 trials. In contrast, injection site reaction was seen in 2-6% of the ITT population for the Phase 3 trials of the 0.25-mg dose. The higher rate of injection site reaction in the 3.0-mg dose might be related to a higher injection volume (3.0 ml in the 3.0-mg dose compared to 1.0 ml in the 0.25-mg dose). All of the injection site reactions consisted primarily of redness, itching and occasionally swelling and all were resolved by 24 hours post-injection.

Cetrorelix antibody formation was reported in studies of the drug for other non-COS/ART indications. In a study of cetrorelix for the treatment of ovarian cancer, one patient displayed an anaphylactic reaction following cetrorelix. No such reaction was seen in the COS/ART studies. This single case will be discussed in the Precautions Section of the label.

The only other patient adverse event that merits discussion is the finding of a modest elevation (1.5 –3 fold) of hepatic transaminases in 1-2% of subjects treated with cetrorelix (even after exclusion of subjects with pre-existing conditions). The clinical significance is unknown. This information will be communicated to the provider in the Precautions Section of the label.

There were 42 twin and 3 triplet pregnancies out of 182 pregnancies in the two dose-finding and three Phase 3 clinical trials giving a multiple gestation rate of 25% which is consistent with that reported for IVF in the SART registries.

There were 3 newborns with major congenital anomalies in these studies. These included one VSD, one anencephalic from a twin gestation (other twin normal) and one case of congenital glaucoma. The percentage of major congenital malformation, 1.34% (3/223 liveborn) is not different from that of the background rate of 2%. The causal relationship of these three anomalies is unknown. There were also three fetal deaths in utero. One of these occurred at 24 weeks and no causality was reported. Maternal conditions (hypertension) were associated with two of the fetal deaths in utero. One of these was also associated with placental abruption.

The data submitted in studies 2986, 2997, 3010, 3020 and 3030 representing a total of 949 subjects on cetrorelix acetate (0.25 mg and 3.0 mg) in COS/ART studies support the safety and efficacy of cetrorelix acetate for the avoidance of premature LH surge in controlled ovarian stimulation for ART. I concur with the recommendation of all the reviewing disciplines that this NDA should be approved.

Label

Most of the major points of labeling negotiations have already been discussed in the preceding sections of this review. One additional point concerns the wording to be used in the Dosage and Administration section with respect to the 3.0-mg dose of cetrorelix in the single dose regimen. The Sponsor intended to develop the single dose regimen for dose administration on day 7 of stimulation. However, in the Phase 3 clinical trial, the injection of cetrorelix was delayed if there was insufficient response to stimulation as judged by an estradiol level less than 400 pg/ml. The cetrorelix dose was then given on the day of stimulation when estradiol exceeded 400 pg/ml. Only 42% of the subjects received the dose on stimulation day 7, the remaining 58% received the dose on stimulation days 5-12. Therefore, it is my opinion that it is misleading to tell the clinician that the single dose should be administered on stimulation day 7 regardless of estradiol level. The new proposed language for administration of the 3.0 mg single dose of cetrorelix in the Dosage and Administration section is "In the single dose regimen, 3.0 mg of Cetrotide™ is administered when the serum estadiol level is deemed sufficient, usually stimulation day 7 (range days 5-12)."

/S/ 8/2/00

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ON ORIGINAL

ASTA MEDICA

FD FORM 356H

Patent Certification

Patent Number: 4,800,191

Expiry Date: July 17, 2007

Type of Patent: Patent for substances, pharm. composition and method of treatment

Name of Patent Owner: The Administrators of the Tulane Educational Fund +)

Name and Address of Agent: Behr & Adams, 325 Pierson Avenue, Edison New Jersey 08837-3123

Original Declaration:
The undersigned declares that patent 4,800,191 covers peptides with high antagonist potency. The claimed formula also contains Cetroreli> The claims also embrace a pharmaceutical composition for reducing the physiological availability of pituitary gonadotropins in a mammal as well as a method of reducing the physiological availability. This patent covers the product, process and method of use for which approval is beeing sought.

Patent Number: 5,198,533

Expiry Date: July 17, 2007

Type of Patent: Patent for substances

Name of Patent Owner: The Administrators of the Tulane Educational Fund +)

Name and Address of Agent: Behr & Adams, 325 Pierson Avenue, Edison New Jersey 08837-3123

Original Declaration:

The undersigned declares that Patent No. 5,198,533 covers some LHRH antagonistic peptide for instance Cetrorelix.This substance is described in example XXVI (26) of the patent 5,198,533.
This patent covers the product for which approval is beeing sought.

Karl-Ludwig Decker

Karl-Ludwig Decker

Senior Patent Specialist

+) The patent is under licensing agreements between the Administrators of the Tulane Educational Fund and ASTA Medica AG consented by the Inventor Prof. Andrew Schally.

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