CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-197

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW(S)

JUL 20 2000

Clinical Pharmacology & Biopharmaceutics Review

NDA:	21-197
Product Trade Name:	CETROTIDE™ (cetrorelix acetate for injection)
Active Ingredient/s:	Cetrorelix acetate
Indication:	Prevention of LH-surges in patients undergoing controlled ovarian stimulation
Submission Dates:	October 29, 1999 (original NDA), 2/23/00 & 7/18/00
Sponsor:	Asta Medica Inc.
Type of Submission/Priority:	Original/1S
Reviewer:	Dhruba J. Chatterjee, Ph.D.
Team Leader:	Ameeta Parekh, Ph.D.

Synopsis

Cetrotide™, (cetrorelix acetate, CET) is a decapeptide with a highly modified LHRH sequence and potent LHRH-antagonistic activity. The sponsor seeks an approval for the use of this drug in the management of LH-surges in patients undergoing controlled ovarian stimulation for *in vitro* fertilization and assisted reproductive technical procedures. Cetrotide™ is formulated as sterile powder for subcutaneous injection in 2 doses, 0.25-mg (QD) and 3.0-mg (once), to be reconstituted with 1-ml and 3-ml water for injections prior to administration, respectively. The 0.25 daily dose is recommended to be started on day 6 or 7 of cycle (day 5 or 6 of stimulation with gonadotropins) and continued until (and including) the day when human chorionic gonadotropin (hCG) is administered (generally day 10 – 11 of cycle). The 3-mg dose is to be administered once on stimulation day 7 (day 8 of cycle). If hCG is not administered within 4 days 3-mg CET injection, 0.25-mg CET should be administered daily until (and including) the day of hCG administration.

A total of 20 studies were submitted in the Human Pharmacokinetic and Bioavailability section of this NDA involving pharmacokinetics in healthy volunteers and patients, as well as pharmacodynamic and dose finding studies. Additional information has also been submitted regarding drug assay.

Recommendation

Based on the review, NDA 21-197 is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective. The suggested labeling changes are included in the section "Labeling Comments" and have been finalized.

/S/

Dated 7/20/2000

Dhruba J. Chatterjee, Ph.D.,
Office of Clinical Pharmacology and Biopharmaceutics (OCPB)
Division of Pharmaceutical Evaluation II

FT signed by Ameeta Parekh, Ph.D. /S/ Dated 7/20/00

C: NDA 21-197, HFD 870 (S. Huang, A. Parekh, DJ. Chatterjee), HFD-580 (G. Willett, J. Best), CDR (B. Murphy).

[A Briefing for NDA 21-197, held on 6/30/2000, was attended by G. Willet, S. Huang, A. Parekh and DJ. Chatterjee]

Table of Contents

APPEARS THIS WAY
ON ORIGINAL

Background

Questions addressed in this section:

- What is the pharmacologic/therapeutic rationale for use of this drug?
- What is the main goal for treatment?
- What are the available treatments?
- What CPB studies have been submitted in support of this NDA?

The reason for unsuccessful achievement of pregnancy may often be related to female factors (e.g. blocked or missing tubes) or male factors (e.g. inadequate sperm motility). One way to overcome such problems is to enroll interested and eligible women to undergo assisted reproductive techniques (ART). Such techniques are preceded by a controlled ovarian hyperstimulation (COS or COH) with repeated injections of human menopausal gonadotropin (hMG), and after approximately 10 days, optimal number and sizes of follicles are observed (with ultrasound). This is followed by a single injection of human chorionic gonadotropin (hCG) for the final maturation of the follicles. Within 36 hours of administration of hCG, mature eggs are surgically removed, fertilized *in vitro*, and placed back in the woman's uterus or fallopian tube (*in vitro* fertilization, IVF). A direct intervention with hMG leads to a rise in serum estradiol (E_2). This results in a subsequent increase in the levels of luteinizing hormone (LH). Such premature rises in LH (also called "LH-surge") results in premature luteinizing and increase in progesterone (P). This may have harmful effects on the quality of oocytes and unfavorable effects on the endometrium, all leading to a reduction of pregnancy rates. Consequently, premature LH-surges are considered to be a reason for cancellation of the treatment cycle. Hence, a major goal of treatment is to minimize the LH-surges.

Luteinizing Hormone Releasing Hormone (LHRH) agonists are often used to manage LH-surges. These act by down regulating the LHRH receptors. Therefore, a long-term treatment is warranted during which an initial stimulation of gonadotropin release ("flare up") for a period of 2-3 weeks is followed by E_2 withdrawal (resulting in hot flushes or premature bleeding). In contrast, pharmacologically, LHRH antagonists compete for LHRH receptors of the pituitary gland and suppress LH immediately, thus conceptually permitting a more physiological prevention of the LH-surge within only a few days of exposure.

Cetrorelix acetate (CET) is a decapeptide (mol. wt. 1431.06) with a highly modified LHRH sequence and potent LHRH-antagonistic activity (binding affinity to LHRH receptor is about 20 times that of LHRH). The drug is formulated as sterile powder for subcutaneous injection as 2 doses, 0.25 mg (QD for 4-5 days in a cycle) and 3.0 mg (once in a cycle), to be reconstituted with 1-ml and 3-ml water for injections, respectively, prior to administration. In this context, in 1999 FDA approved Ganirelix acetate (Antagon®), another decapeptide LHRH-antagonist for the same indication. The approved dose of Antagon® is 0.25 mg QD.

In this NDA, the sponsor has submitted data from 20 clinical pharmacology and biopharmaceutics studies describing ADME (males and females) and dose finding (females) aspects for the drug.

This review follows a 'Question-Based' approach.

In a multiple dose ***Study 0008*** in a total of 19 (evaluated) patients, several dosing schedules – 1 mg CET daily, 3 mg CET daily, 3 mg and then 5 mg, 3 mg and then 1 mg – were investigated. The main conclusion of the study was that, LH-surge was controlled adequately and similarly from 1 or 3 mg doses. The effect of CET on LH levels showed no obvious dose-dependency in the range of 1 mg to 3 mg; the effect of 1 mg and 3 mg were sustained, allowing once daily administrations. There was no evidence of an effect of CET upon FSH, PROG or E_2.

Study 0012 was conducted in 22 patients undergoing COS. Initially, a 1-mg CET dose was given QD to one group, and with no signs of LH-surges, the second group was given a daily dose of 0.5-mg CET. None of the patients in either group experienced a LH-surge during CET treatment. 3 patients who were excluded from the efficacy criteria did not show LH-surge as well. Figures below describe the effect on LH (Figures 6a and b).

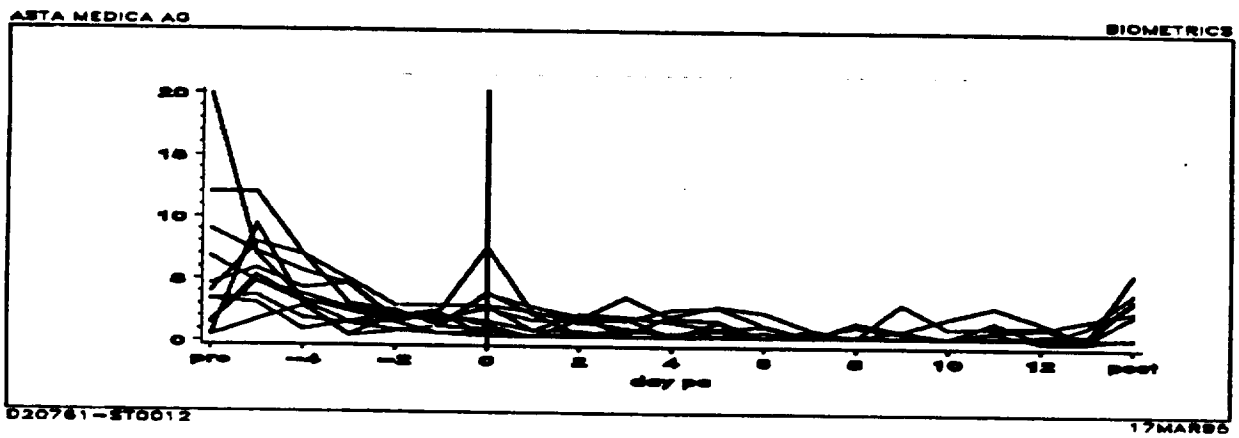

Figure 6a: Individual courses of LH (IU/l) for the CET 1-mg dose group - CET started on day 0

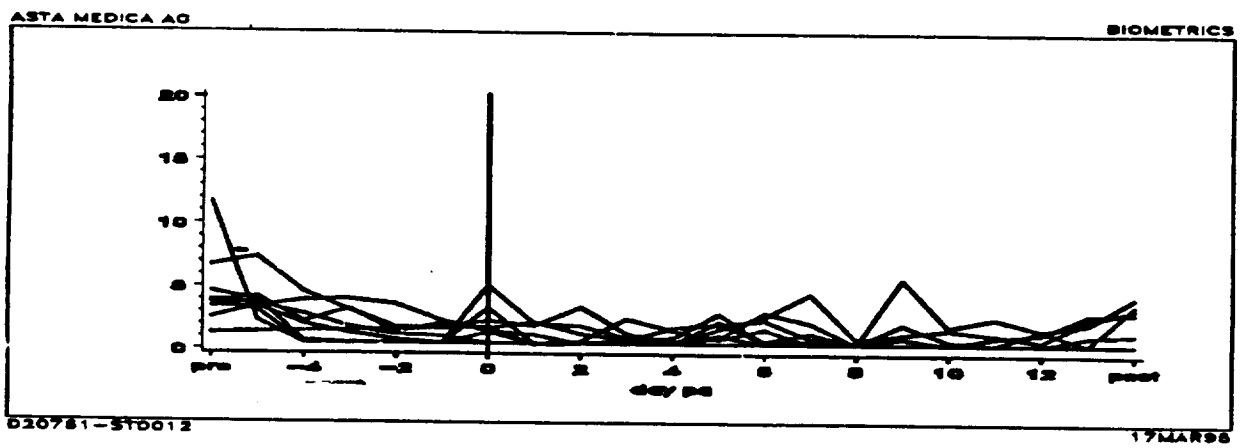

Figure 6b: Individual courses of LH (IU/l) for CET 0.5-mg dose group -CET started on day 0

This study shows that both the 1-mg and 0.5-mg daily doses of CET were equally effective in management of LH-surge in the patients, and a dose-related effect was not observed. There was no trend of an effect on FSH, P or E_2. The sponsor evaluated a high success rate for the study. CET plasma levels were < 2.0 ng/ml on the days of OPU and ET.

Q. Is the sponsor's selection of dose and regimen justified?

As evident from the pharmacodynamic studies, CET is effective from 5-mg and 3-mg single doses, as well as 3-mg, 1-mg, and 0.5-mg multiple doses. In order to optimize the single and multiple dosing amounts (and regimen), the sponsor conducted two "dose-finding" studies.

Study 2986 was conducted in patients undergoing COS to evaluate whether a single 3-mg, 2-mg or even lower doses be adequate to manage LH-surges. Therefore, study was designed to determine the optimal single dose.

The results of this study confirm that single SC injections of 2 to 3 mg CET may effectively suppress LH levels in patients undergoing COS for ART, without interfering with the hormones FSH, E2, or PROG. A single injection of 3 mg was able to prevent premature LH surge in all 34 patients treated with this dose, and in all except one patient, mature oocytes could be retrieved. One case, possibly representing a LH surge, occurred in the 2-mg group. In another patient, the 2-mg CET dose was not able to control LH levels for a sufficiently long duration, and a second dose was administered. Furthermore, median LH profiles indicate that the LH levels of patients treated with the 2-mg dose tend to re-increase after 3 days, while the LH levels of patients treated with 3 mg did not. Thus, it was concluded that a single injection of 2 mg CET does not guarantee the prevention of premature LH surges for more than 3 days. In contrast, single injections of 3 mg CET may reliably prevent a premature LH surge for at least 4 days. Figure 7 shows the nature of LH-suppression with 2 and 3-mg doses. Figure 8 and Table 9 describes the PK of CET obtained from this study.

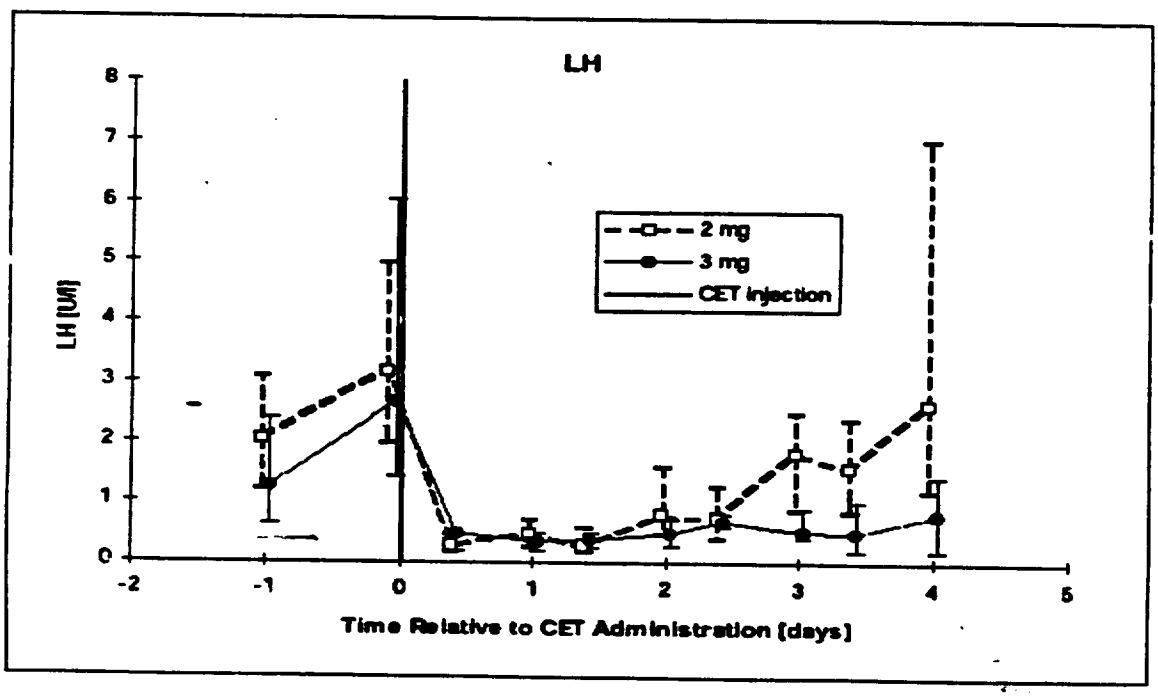

Figure 7: LH levels, Medians Together with the Interquartile Ranges [Note: At least up to about 36 hours after the CET injection, there was no difference between the two treatment groups. Three days after CET administration, the two curves were split indicating a slight resurgence of the LH levels in the 2-mg dose group only]

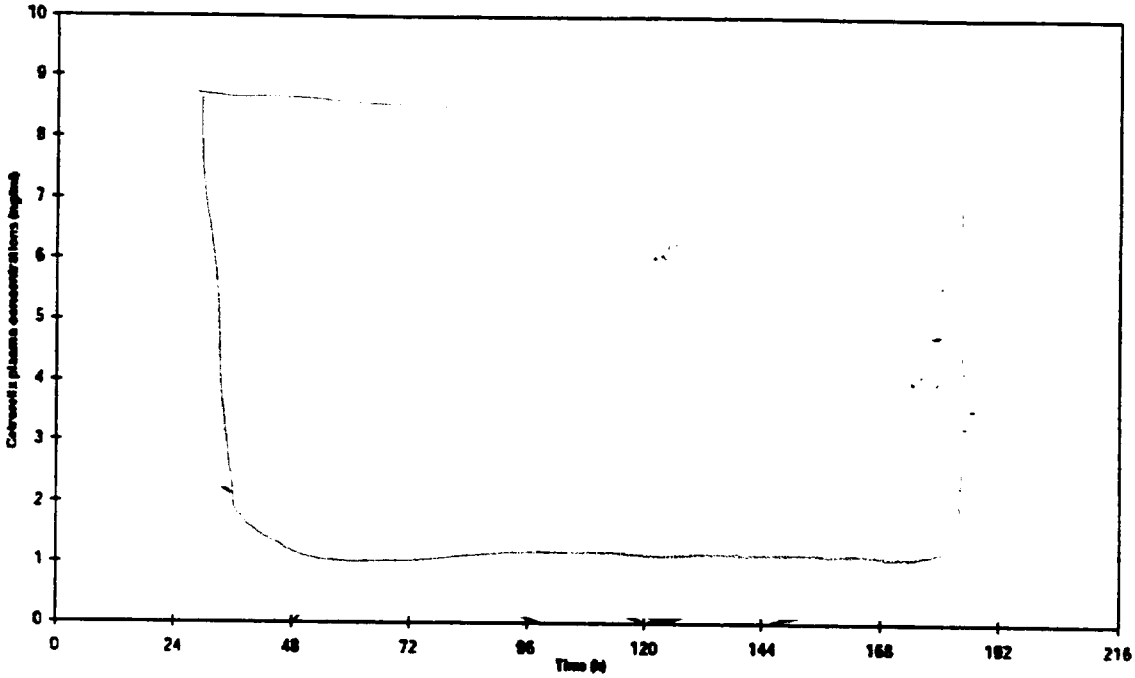

Figure 8: Individual plasma concentrations of CET, following single doses of 3 mg

Table 9: Relevant PK parameters of CET

		Dose: 2 mg CET	Dose: 3 mg CET
Elimination half-life			
Median	[h]	48.8	62.2
Min	[h]	—	—
Max	[h]	—	—
N		22	26
Ratio $C_{follicle}/C_{plasma}$ at the time of OPU			
$Mean_{geo}$	[ng/ml]	0.85	0.90
95% CI_{in}	[ng/ml]	0.62 - 1.17	0.79 - 1.01
N		5	17
C_{plasma} at the time of OPU			
Lower quartile	[ng/ml]	0.45	0.56
Median	[ng/ml]	0.61	0.74
Upper quartile	[ng/ml]	0.80	0.92
N		30	22
$C_{follicle}$ at the time of OPU			
Lower quartile	[ng/ml]	0.16	0.55
Median	[ng/ml]	0.29	0.69
Upper quartile	[ng/ml]	0.39	0.90
N		26	27
C_{plasma} at the time of ET			
Lower quartile	[ng/ml]	0.24	0.41
Median	[ng/ml]	0.26	0.53
Upper quartile	[ng/ml]	0.42	0.68
N		9	17

Study 2997 was an open-label sequential group trial. The dosages were to be given in strict consecutive order until occurrence of LH-surge or until reaching the planned maximum group size of 30 subjects without occurrence of LH-surge. Then the next higher (in case of a LH surge) or lower dosage group (in case that no LH surge occurred) was to be started. The starting dose was 0.5 mg per day. In case of down-titration - the dose steps foreseen were 0.25 mg and 0.1 mg. This study was basically designed to find the lowest CET daily dose that may be used (multiple doses between cycle days 7 – 10/11) that can manage LH-surges.

The study showed that the minimum dose that could manage LH-surges in 100% of the cases was 0.25-mg. At the 0.1-mg level, one patient experienced a LH-surge during treatment with CET. This lead to cancellation of the dose group, and the patients assigned to this group were transferred to the 0.25-mg group, and no LH-surge was observed. Please refer to Figure 9 below:

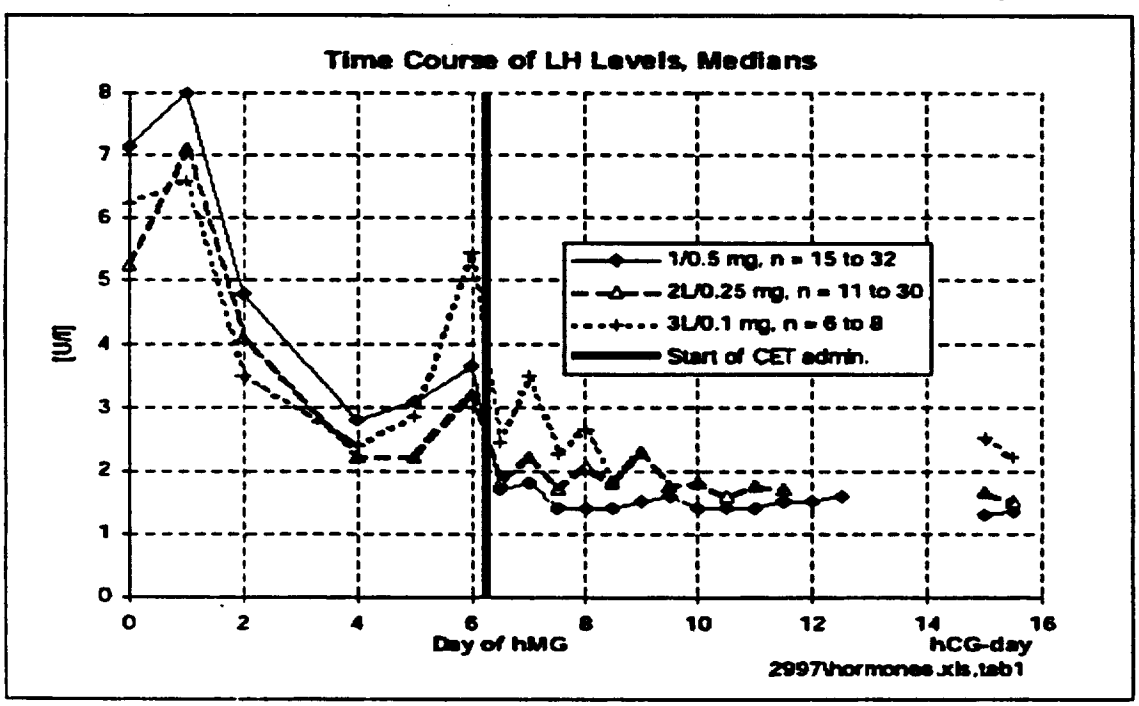

Figure 9: LH time course [Time points with less than half the number of observations of the full group size, and the groups 3L/0.1/0.25 mg and 3L/0.25 mg are not included.]

Considering the finding in all these studies, it might be concluded that the sponsor's dose selection plan was well designed and thorough. Adequate studies were performed to optimally identify both the single (higher) dose - 3.0-mg, and the multiple (lower) dose – 0.25-mg. The selection of these two doses gives the physician a choice of regimens – either one 3-mg dose, or a daily 0.25-mg dose. Moreover, following a 3-mg single dose, if sonography results (follicle sizes) and E_2 levels indicate a delay in administration of HCG, then additional doses of 0.25-mg CET may be used till necessary.

Serum level of CET on days of OPU and ET were all < 2.5 ng/ml from the 3-mg (higher) dose. The shortest interval between the last CET and when the embryo may be exposed to CET is > 4 days and the serum levels may be even lower. Although these CET levels may appear

insignificant, the effects (from these levels) on the embryo or resulting in hormonal imbalances during pregnancy (following IVF and ET) are not determinable from the information submitted.

Q. Was PK of CET studied in special populations? Was there any population-PK analysis?

No. CET is intended to be used in healthy young women, and patients with hepatic/renal impairment will not use this drug. Thus, absence of such information is not critical.

The sponsor has not performed any population pharmacokinetic analysis in the Phase III studies. No information was submitted regarding the relationship of PK parameters to demographic factors. The Medical Officer noted that in an overweight (100 kg) patient (pivotal study 3010, center 24, patient 34), CET was < LOQ in the serum following a 0.25-mg dose, and a rise in LH and P were observed. The explanation might be that, in the absence of body-weight correction with dosing, the drug in this patient was diluted to a larger volume of plasma.

On our request, the sponsor submitted a correlation analysis of certain PK parameters with weight and BMI in their Phase II PK and PD studies (submission dated June 7, 2000). In general, the correlation coefficients were weak (-0.5 to +0.5). However, in one study (3031), a stronger correlation between $AUC_{0\text{-last}}$ and body weight was observed for the 0.25-mg dose group (correlation coefficient – 0.78). However, with the limited data available, no definitive conclusions should be made. Consequently, no dose adjustment is recommended.

Q. Has the sponsor addressed the issue of a potential metabolic drug-drug interaction?

CET is a peptide, and is expected to be metabolized by peptidases prior to be presented in the liver. Moreover, there is no evidence that CET is metabolized by CYP 450 enzymes. Hence, the sponsor did not conduct specific studies to determine metabolic drug interactions, and this is acceptable.

Q. Are there any proposed changes in formulation?

No. The sponsor has indicated in a facsimile (see attachment 1) that there will be no difference in the formulation intended for the market than the one evaluated in the clinical trials.

Q. Are the analytical method described for the drugs acceptable?

RIA and HPLC assay methods were used to determine plasma concentration of CET (and peptidic metabolites). The sponsor has described both the procedures in details and has provided the necessary validation reports. For the PK and PD studies (described in this review), accuracy values ranged from – 25% to 25% (typical values were 8% to 15%); precision values ranged between 9% - 30% (typical values were 7 – 15%). The higher deviations were generally observed from the lower concentrations. Attachment 2 provides more details on the analytical methods used for each study, and the respective LOQ values. The analytical methods used for the PK and PD studies are acceptable.

Number of Pages Redacted 3

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Draft Labeling
(not releasable

Attachment 1

FAX

ASTA MEDICA

ASTA Medica, Inc.

FROM

Date: December 3, 1999

Brian A. Green
Phone: (978) 851-5981 ext 220 Fax: (978) 851-5917
e-mail: bgreen@MuroPharm.com

TO

Ms. Jeanine Best, Project Manager
Division of Reproductive and Urologic Drug Products (HFD-580)
Office of Drug Evaluation II, CDER, FDA
Fax Number: (301) 827-4267

No of Pages: 3

RE: **Information concerning the formulation of clinical trial batches and the formulation of batches intended for the market for CETROTIDE™; NDA 21-197**

Dear Ms. Best:

Reference is made to our October 28, 1999 submission of a New Drug Application for CETROTIDE™ (cetrorelix acetate for injection) 0.25 mg and 3 mg, for the prevention of premature ovulation in patients undergoing controlled ovarian stimulation, which is identified as NDA 21-197.

In addition, reference is made to a telephone conversation between you and myself during which information was requested about any changes in formulation between the clinical trial batches and the batches intended for the market.

The purpose of this fax is to inform you that there is no difference in the formulation of the clinical trial batches and the batches intended for the market. Attached please find page 365 from Volume 1.1, which shows the formulation of the batches intended for the market. Also attached please find a copy of page 377 from Volume 1.1, which shows the formulation of the clinical trial batches.

I hope this information is useful; I apologize for any inconvenience we may have caused by not pointing this out more clearly in the application. If you have any questions about this application or need any additional information, please feel free to contact me at the number above, or Dr. Ingeborg Arny, Senior Regulatory Associate, at ext. 403.

Sincerely,

Brian A. Green

Brian A. Green

Number of Pages Redacted 1

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Confidential,
Commercial Information

DF DEC - 8 1999

FILING MEMORANDUM

NDA#:	21-197
Product/Active Ingredient/s:	Cetrotide™ 0.25 & 3 mg (cetrorelix acetate for injection)
Indication:	Prevention of premature ovulation in patients undergoing controlled ovarian stimulation
Submission Date:	October 28, 1999
Sponsor:	ASTA MEDICA, Inc.
Type of Submission:	Original NDA
Reviewer:	Dhruba J. Chatterjee, Ph.D.
Today's Date:	December 3, 1999

Synopsis

Cetrotide™ (cetrorelix acetate for injection) is a synthetic decapeptide with a sequence homology to LHRH and a high specificity towards LHRH antagonistic activity. The proposed label for this product indicates that the sponsor wishes to market two doses, 0.25 and 3.0 mg. In the two dosage forms, Cetrotide™ will be available as a sterile lyophillized powder for subcutaneous injection after reconstitution with Sterile Water for Injection, USP (supplied in pre-filled syringes). Each vial will contain the equivalent sterile Cetrotide™ powder (0.25 or 3.0 mg) and required amount of mannitol (for tonicity). The product is indicated to be used in women for the prevention of premature ovulation in patients undergoing controlled ovarian stimulation. Cetrorelix is a new molecular entity.

The sponsor, in this application, reports a total of 17 studies involving clinical pharmacokinetics of cetrorelix (please refer to attachment I for a categorical listing). This includes 11 Phase I studies in females and males involving safety and tolerability from both single and multiple doses. The 6 Phase II studies reported are mostly proof of concept and dose finding PK studies. Additionally, information from studies is also included regarding the absolute bioavailability of cetrorelix, metabolism, mass balance etc.

Two analytical methods (using either the HPLC or radioimmunoasaasy) for detection of cetrorelix in biological fluids (human serum, urine, bile, follicular fluid) are described and results and method validations are included in the submission.

The manufacturing process as well as the drug formulation used in the clinical trials have (and will have) essentially remained the same for the to-be-marketed product (see attachment of facsimile communication).

Studies on special population (hepatic/renal disease, or elderly patients), or specific drug-drug interaction studies have not been conducted. It may be pointed out that young healthy women will particularly use the product. Additionally, the drug is expected to be primarily metabolized by peptidases and not by liver enzymes. However, these are labeling related review issues.

Recommendation

This NDA is fileable from a Clinical Pharmacology and Biopharmaceutics perspective. No comments need to be sent to the sponsor at this time.

/S/

Date 12/8/99

Dhiraba J. Chatterjee, Ph.D.
Pharmacokinetics Reviewer
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation II

FT Signed by Ameeta Parekh, Ph.D. (Team Leader) /S/ Date 12/8/99

APPEARS THIS WAY
ON ORIGINAL

CC: NDA 21-19739, HFD-870 (M. L. Chen, A. Parekh, D.J. Chatterjee), HFD-580 (J. Willet, J. Best), CDR (E. Murphy).

ASTA MEDICA

ASTA Medica, Inc.

NEW DRUG APPLICATION
FDA FORM 356H
(Attachment I)

CETRORELIX ACETATE FOR INJECTION

PHARMACOKINETIC DATA

Contained in this section are the following:

Table of Contents – Reports of pharmacokinetic studies

Integrated Summary of Pharmacokinetic studies (included in this volume behind the Table of Contents) *(including a table of all pharmacokinetic studies, summary tables of data, and tables of formulations)*

The Pharmacokinetic Studies included in this NDA are listed below with the volume number included, as follows:

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CETRORELIX ACETATE FOR INJECTION

PHARMACOKINETIC DATA

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CETRORELIX ACETATE FOR INJECTION

PHARMACOKINETIC DATA

ASTA MEDICA

ASTA Medica, Inc.

CETRORELIX ACETATE FOR INJECTION

PHARMACOKINETIC DATA

(Attachment II)

FAX

ASTA MEDICA

ASTA Medica, Inc.

FROM

Brian A. Green
Phone: (978) 851-5981 ext 220
e-mail: bgreen@MuroPharm.com

Date: December 3, 1999

Fax: (978) 851-5917

TO

Ms. Jeanine Best, Project Manager
Division of Reproductive and Urologic Drug Products (HFD-580)
Office of Drug Evaluation II, CDER, FDA
Fax Number: (301) 827-4267

No of Pages: 3

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Sincerely,

Brian A. Green

Brian A. Green

CETRORELIX ACETATE FOR INJECTION

CLINICAL & STATISTICAL DATA

Title: Overuse and Drug Abuse Section

Cetrorelix acetate is not a drug that is subject to abuse. There is no known antidote to cetrorelix.