ASTA MEDICA

NDA 21-197
CETROTIDE™ (cetrorelix acetate for injection)

June 9, 2000

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

Telephone 978.851.5981
Telefax 978.851.7346

Susan Allen, MD, Acting Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Office of Drug Evaluation III, CDER, FDA
5600 Fishers Lane
Rockville, MD 20852

ORIG AMENDMENT
BL

Re: Response to June 2, 2000 and June 6, 2000 Request for Information

Dear Dr. Allen:

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

Reference is also made to a June 2, 2000 telephone conversation between myself and Ms. Jeanine Best from your Division, during which Ms. Best relayed a request from the Medical Review Officer to provide the approved labeling from the United Kingdom. In addition, reference is made to a June 6, 2000 telephone conversation between Ms. Best and myself wherein the Division requested that we combined our two proposed package inserts (one for each strength) into a single package insert.

Enclosed please find a copy of the English language version of the approved labeling for the European Union. There is no separate labeling for the United Kingdom. This includes a copy of the Summary of Product Characteristics text (used by healthcare professionals), the label and carton texts, and the Package Leaflet text. A copy of the Package Leaflet showing the layout is also included. In addition, our proposed package inserts have been combined into one package insert. All labeling text is included on a floppy disk as MS Word Files.

If you have any questions or require any additional information concerning the information in this submission, please contact me at (978) 858-2553, or Roberta Tucker, RPh, Director of Regulatory Affairs, at (978) 858-2656.

Sincerely,

Brian A. Green

Brian A. Green
Manager
Regulatory Affairs

ORIGINAL

NDA 21-197
CETROTIDE™ (cetrorelix acetate for injection)

June 7, 2000

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

Telephone 978.851.5981
Telefax 978.851.7346

Susan Allen, MD, Acting Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III, CDER, FDA
HFD-580
5600 Fishers Lane
Rockville, MD 20852

ORIG AMENDMENT
BM

Re: Response to May 2, 2000 Request for Information

Dear Dr. Allen:

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

In addition, reference is made to a May 2, 2000 telephone conversation between myself and Ms. Jeanine Best from your Division, during which Ms. Best relayed a request from the Medical Review Officer to provide the following information in SAS format for each patient in Studies 3010, 3020 and 3030: study number, center number, subject number, weight (kg), dosage amount, date of visit, lower limit of quantification, and blood levels of cetrorelix.

Reference is also made to a follow-up conversation with Ms. Best on May 8, during which I informed Ms. Best that blood levels were not routinely obtained for patients in the Phase III studies. Ms. Best indicated that we should provide the requested information for Phase II studies if blood levels were routinely measured in those studies. Enclosed please find our response (in paper and on CD-ROM) to this request for information.

If you have any questions or require any additional information concerning the information in this submission, please contact me at (978) 858-2553, or Roberta Tucker, RPh, Director of Regulatory Affairs, at (978) 858-2656.

Sincerely,

Brian A. Green

Brian A. Green
Manager
Regulatory Affairs

REVIEWS COMPLETED

ORIGINAL

NDA 21-197
CETROTIDE™ (cetrorelix acetate for injection)

June 6, 2000

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

Telephone 978.851.5981
Telefax 978.851.7346

Susan Allen, MD, Acting Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III, CDER, FDA
HFD-580
5600 Fishers Lane
Rockville, MD 20852 ORIG AMENDMENT

Re: Response to April 27, 2000 Request for Information

Dear Dr. Allen: BM

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

In addition, reference is made to an April 27, 2000 telephone conversation between myself and Ms. Jeanine Best from your Division, during which Ms. Best relayed a request from the Medical Review Officer to provide historical pregnancy rate data from selected sites in our three Phase III pivotal studies. Enclosed please find our response to this request for information.

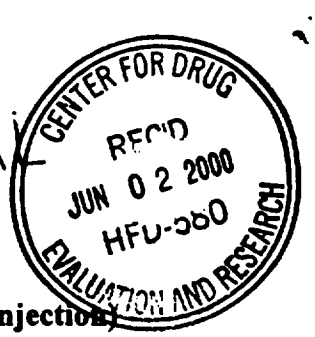
If you have any questions or require any additional information concerning the information in this submission, please contact me at (978) 858-2553, or Roberta Tucker, RPh, Director of Regulatory Affairs, at (978) 858-2656.

Sincerely,

Brian A. Green

Brian A. Green
Manager
Regulatory Affairs

ORIGINAL



ASTA MEDICA

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

Telephone 978.851.5981
Telefax 978.851.7346

NDA 21-197
CETROTIDE™ (cetrorelix acetate for injection)

June 1, 2000

Susan Allen, MD, Acting Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III, CDER, FDA
HFD-580
5600 Fishers Lane
Rockville, MD 20852

ORIG AMENDMENT

BC

Re: Response to Discipline Review Letter dated April 4, 2000

Dear Dr. Allen:

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

In addition, reference is made to a Discipline Review Letter from the Division dated April 4, 2000, which contained Chemistry, Manufacturing and Controls comments. Enclosed please find a complete response to the Division's April 4, 2000 letter.

Since this product is manufactured outside the United States, the complete field copy of this submission will be submitted in parallel to Ms. Rochelle Kimmel, Division of Emergency Investigational Operations, as directed by the Boston District Office.

If you have any questions or require any additional information concerning the information in this submission, please contact me at (978) 858-2553, or Roberta Tucker, RPh, Director of Regulatory Affairs, at (978) 858-2656.

Sincerely,

Brian A. Green

Brian A. Green
Senior Regulatory Affairs Associate

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

ORIGINAL

NDA 21-197
CETROTIDE™ (cetrorelix acetate for injection)

May 22, 2000

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

Telephone 978.851.5981
Telefax 978.851.7346

Susan Allen, MD, Acting Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III, CDER, FDA
HFD-580
5600 Fishers Lane
Rockville, MD 20852

ORIG AMENDMENT

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAY 23 2000
HFD-580

BB

Re: Electronic Copies of Pharmacokinetic Reports
Change in Correspondence

Dear Dr. Allen:

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

Reference is also made to an April 18, 2000 conversation with Ms. Jeanine Best, who relayed a request from the Biopharmaceutics Reviewer for an electronic copy of the Pharmacokinetic study reports. Enclosed please find, in duplicate, a CD-ROM which contains the requested information. Please note that there are two versions of Study 3124: a preliminary PK report (which was included in the original NDA) and the finalized clinical trial report (which was included as an attachment with the 4-month safety update).

In addition to this submission of information, we would like to request that all future written correspondence be addressed to the undersigned.

If you have any questions or require any additional information concerning the information in this submission, please contact me at (978) 858-2553, or Roberta Tucker, RPh, Director of Regulatory Affairs, at (978) 858-2656.

Sincerely,

Brian A. Green

Brian A. Green
Senior Regulatory Affairs Associate

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

ORIGINAL

NDA 21-197
CETROTIDE™ (cetrorelix acetate for injection)

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

Telephone 978.851.5981
Telefax 978.851.7346

May 18, 2000

Susan Allen, MD, Acting Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III, CDER, FDA
HFD-580
5600 Fishers Lane
Rockville, MD 20852

Re: Additional Preclinical Data

ORIG AMENDMENT

BM

Dear Dr. Allen:

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

Our initial NDA included four acute toxicity studies: two studies in mice and two studies in rats (one oral administration and one intraperitoneal administration for each species). In addition, local irritation studies were performed in Beagle dogs by intravenous, intraarterial, paravenous, subcutaneous and intramuscular routes of administration.

As discussed with Ms. Jeanine Best from your Division on May 9, 2000, it has recently come to our attention that the following additional preclinical studies were performed for cetrorelix (a.k.a. NS75A in Japan) and were inadvertently not included in our initial NDA:

1. A single subcutaneous toxicity study of NS75A in rats and associated toxicokinetic study.
2. A single subcutaneous toxicity study of NS75A in dogs.
3. Antigenicity study of NS75A in mice.
4. Antigenicity study of NS75A in guinea pigs.
5. Orientating Maximum Tolerated Dose (MTD)-finding study and plasma level determination after repeated subcutaneous administration in mice.
6. Orientating MTD-finding study and plasma level determination after repeated subcutaneous administration in rats.

7. MTD-finding study by s.c. administration (twice weekly; 26 weeks) in mice with an associated toxicokinetic report.
8. MTD-finding study by s.c. administration (daily; 26 weeks) in mice with an associated toxicokinetic report.
9. MTD-finding study by s.c. administration (twice weekly; 26 weeks) in rats with an associated toxicokinetic report.
10. MTD-finding study by s.c. administration (daily; 26 weeks; 6 week recovery) in rats with an associated toxicokinetic report.
11. Acute toxicity after single intravenous administration in mice.
12. Acute toxicity after single intravenous administration in rats.
13. Toxicological examination after single intravenous administration in rats (pretreated with orally administered Azelastine HCl)
14. Toxicological examination after single intravenous administration in rats (pretreated with orally administered Cyproheptadine (Peritol®)).
15. A local tolerability study after single intramuscular & subcutaneous injection in rabbits.
16. A local tolerability study after single intramuscular & subcutaneous injection in beagles.
17. A local tolerability study after repeated intramuscular & subcutaneous injection in beagles

Studies 1-2 were conducted by . **Studies 3-4** were conducted by . These four studies were performed by partner companies for local requirements, but they were not conducted at the request of ASTA Medica, Inc. nor ASTA Medica AG (our parent company). **Studies 5-6** were pilot studies used to help define the appropriate doses for use in the MTD-finding studies.

The MTD-finding studies (**Studies 7-10**) were initially performed to identify the optimal dosage for planned carcinogenicity studies. The carcinogenicity studies were cancelled, because no long-term treatment is planned for Cetrorelix acetate that would require carcinogenicity studies according to ICH guidelines. Therefore, the MTD-finding studies were experimentally finished, the raw data archived and final reports were not written.

Although there were no substance-related systemic toxicological findings in the MTD-finding studies, a granuloma-like reaction was observed at the injection site. Subsequent injections of Cetrorelix solution into the vascularized granuloma tissue effectively resulted in a quasi-intravenous injection. This quasi-intravenous injection led to mast cell degranulation with subsequent clinical symptoms of hypotensive shock and eventually, death. A summary of these MTD-finding studies is included in this submission.

Because of the findings above, acute toxicity studies in mice and rats (**Studies 11-12**) after single intravenous administration were performed to reconfirm the assessment of the MTD-finding studies. In both acute i.v. toxicity studies, all animals at the highest dose levels died within hours of cetrorelix administration. In mice, mid-dose animals were treated with two different concentrations of solution (1 mg/mL and 2 mg/mL); no mice treated with the dilute solution died, whereas all mice treated with the concentrated solution died.

In order to confirm that there was no histamine release (which is a known phenomenon for first generation LHRH antagonists), two additional studies in rats were conducted to see whether the histamine H_1 antagonist Azelastine HCl (**Study 13**) or the serotonin antagonist Cyproheptadine (**Study 14**) could protect animals from lethality induced by Cetrorelix.

Based on the results of these studies, it can be concluded that Cyproheptadine is able to protect the rats from lethality, but a potent histamine H_1-antagonist has no influence on the rate of mortality. Therefore, a histamine release can be excluded as an inductor of the lethality induced by Cetrorelix. However, serotonin has a major role in the pathogenesis of the diagnosed clinical and histopathological signs, which occurred after intravenous administration in the rat.

It is important to note that this serotonin-releasing phenomenon is restricted to relatively high **intravenously** administered doses of cetrorelix in rats. Unlike histamine, there is a marked species heterogeneity of the presence of serotonine in mast cells. Histamine and serotonin may undergo a differential release from mast cells. In contrast to the rat, human mast cells are not able to store serotonin. Therefore, the observed findings in this model system are not relevant for the intended use in humans.

Finally, **Studies 15-17** were conducted with cetrorelix acetate using a solution concentration of 2.5 mg/mL. These studies were conducted to support the development of a depot formulation to be used for different indications than the indication sought in this NDA.

The results of the above referenced studies do not negatively impact the safety profile of CETROTIDE™ for the claimed indication (the prevention of premature ovulation in patients undergoing controlled ovarian stimulation) and no revisions to the proposed package insert based on these studies is required.

Reports for the studies conducted in Japan (**Studies 1-4**), the pilot MTD and plasma level determination studies (**Studies 5-6**), the acute IV toxicity studies (**Studies 11-14**), and the studies using a concentration of 2.5 mg/mL (**Studies 15-17**) are included in this submission.

A summary of the maximum tolerated dose finding studies (**Studies 7-10**) is also included. Final reports for the MTD-finding studies and the related toxicokinetic reports will be available for submission in June.

In addition to the preclinical studies above, a number of preclinical reports for studies using a different salt are being submitted as an information amendment to [redacted]. A list of these studies is attached. Please note that these studies have no impact on this NDA.

If you have any questions or require any additional information concerning the information in this submission, please contact me at (978) 858-2553, or Roberta Tucker, RPh, Director of Regulatory Affairs, at (978) 858-2656. Please note that these are new telephone numbers.

Sincerely,

Brian A. Green

Brian A. Green
Senior Regulatory Affairs Associate

APPEARS THIS WAY
ON ORIGINAL

REVIEWS COMPLETED

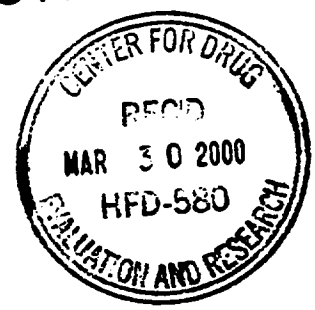
CONCLUSION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

ORIGINAL

ORIG AMENDMENT

BC



ASTA MEDICA

March 29, 2000

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

Telephone 978.851.5981
Telefax 978.851.7346

Lisa Rarick, MD, Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II, CDER, FDA
HFD-580
5600 Fishers Lane
Rockville, MD 20852

Re: CETROTIDE™ (cetrorelix acetate for injection)
NDA #21-197
Stability Data (0.25 mg strength)

Dear Dr. Rarick:

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 our initial NDA, supportive stability data was provided for batches manufactured using an older lyophilization process and using drug substance manufactured solely at [redacted]. Primary stability batches were manufactured using a slightly modified lyophilization process and using drug substance that was deprotected and purified at [redacted]. Also included in the application were stability protocols for the primary stability batches (3 batches each of the 0.25 mg and 3 mg strengths).

Enclosed please find a stability report for 6 months stability data of the 0.25 mg strength. A copy of this submission is also being sent to the New England District Office.

If you have any questions or require any additional information concerning the information in this submission, please contact me at (978) 858-2553, or Roberta Tucker, RPh, Director of Regulatory Affairs, at (978) 858-2656. Please note that these are new telephone numbers.

Sincerely,

Brian A. Green

Brian A. Green
Senior Regulatory Affairs Associate

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS DATE

ASTA MEDICA

March 9, 2000

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

Telephone 978.851.5981
Telefax 978.851.7346

Lisa Rarick, MD, Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II, CDER, FDA
HFD-580
5600 Fishers Lane
Rockville, MD 20852

Re: CETROTIDE™ (cetrorelix acetate for injection)
NDA #21-197
4 Month Safety Update (electronic version)

SU

Dear Dr. Rarick:

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.

Reference is also made to our February 29, 2000 submission of the 4-month safety update. In the cover letter of this submission, ASTA Medica stated that an electronic version of the safety update would be submitted in electronic format.

Enclosed please find 2 CD-ROMs each containing an electronic copy of the ISS amendment, the updated Pregnancy, Delivery and Baby Follow-Up Data report, and associated datasets. Please note that the clinical trial reports for the three reported studies are not included, since they were either Phase I or Phase II studies.

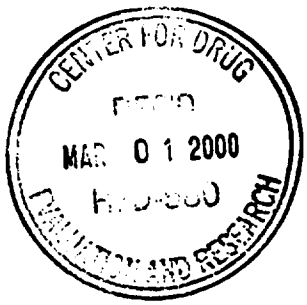
If you have any questions or require any additional information concerning the information in this submission, please feel free to contact me at (978) 851-5981, ext. 220 or Roberta Tucker, RPh, Director of Regulatory Affairs, at ext. 356.

Sincerely,

Brian A. Green

Brian A. Green
Senior Regulatory Affairs Associate

ORIGINAL



ASTA MEDICA

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

Telephone 978.851.5981
Telefax 978.851.7346

February 29, 2000

Lisa Rarick, MD, Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II, CDER, FDA
HFD-580
5600 Fishers Lane
Rockville, MD 20852

SU

Re: CETROTIDE™ (cetrorelix acetate for injection)
NDA #21-197
4 Month Safety Update

Dear Dr. Rarick:

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 accordance with 21 CFR §314.50(d)(5)(b)(1), we are submitting a 4 month safety update. This safety update includes safety data from three clinical trials as well as safety data from ongoing studies and studies in different indications. There is no change in the safety profile of Cetrotide™; no changes to the draft labeling provided in the NDA are necessary.

This amendment to the Integrated Summary of Safety (ISS) contains the same type of information and is in the same format as the ISS provided in the initial NDA (Volumes 129-130 of the Clinical Data Section). In addition, we are including three clinical trial reports which constitute the integrated safety database in the ISS amendment.

We are also providing an update to our Pregnancy, Delivery and Baby Follow-Up Data report (Volume 125 of the Clinical Data Section).

Please note that ~~in the~~ original NDA, Case Report Forms (CRF's) were provided for patients who died or discontinued due to an adverse event for those studies which constituted the integrated safety database. CRF's were not provided for patients who died or discontinued due to an adverse event from studies designated as secondary sources (i.e., ongoing or not reported for COS/ART studies or for different indications). For consistency, no CRF's are included with this safety update, as no patients died or discontinued due to an adverse event in the three clinical trials which constitute the integrated safety database.

An electronic copy of the ISS amendment, the updated Pregnancy, Delivery and Baby Follow-Up Data report, and the three clinical trial reports will be submitted in the near future.

If you have any questions or require any additional information concerning the information in this submission, please feel free to contact me at (978) 851-5981, ext. 220 or Roberta Tucker, RPh, Director of Regulatory Affairs, at ext. 356.

Sincerely,

Brian A. Green

Brian A. Green
Senior Regulatory Affairs Associate

APPEARS THIS WAY
ON ORIGINAL

ASTA MEDICA

December 23, 1999

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

Telephone 978.851.5981
Telefax 978.851.7346

Lisa Rarick, MD, Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Office of Drug Evaluation II, CDER, FDA
Room 17B-45
5600 Fishers Lane
Rockville, MD 20852

ORIG AMENDMENT
BM

ORIGINAL

Re: CETROTIDE™ (cetrorelix acetate for injection)
NDA #21-197
INFORMATION REGARDING CLINICAL SITES

Dear Dr. Rarick:

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 myself and Roy Blay from the Division of Scientific Investigation, during which information was requested about the study sites in the pivotal Phase III clinical trials for the above referenced NDA. Specifically, the names and the addresses of the principal investigators for each site where requested, as well as the number of patients enrolled per site, the number of completed patients per site, and the number of serious adverse events per site.

The purpose of this submission is to provide the requested information in tabular form for studies 3010, 3020, and 3030. The information is presented as follows:

- The first column contains the name of the investigator and the center number.
- The second column contains the address for each investigator.
- The third column lists the number of patients enrolled, and the number of patients who completed treatment with study drug (either cetrorelix, buserelin or triptorelin, depending on study) **and** treatment with human chorionic gonadotropin (hCG).
- The fourth column represents patients who did not complete because: a) study drug was not administered, b) hCG was not administered, c) oocyte pick or assisted reproductive technique failed. The sum of patients listed for reasons (a) and (b) represents the difference between patients enrolled and patients completed shown in the third column
- The fifth column shows the number of serious adverse events for each site.

A copy of this information was faxed to Mr. Blay today; a hardcopy of this information will also be sent to Mr. Blay.

If you have any questions or require any additional information concerning the information in this NDA, please feel free to contact me at (978) 851-5981, ext. 220 or Dr. Ingeborg Army, Senior Regulatory Associate, at ext. 403.

Sincerely,

Brian A. Green

Brian A. Green
Senior Regulatory Affairs Associate
ASTA Medica, Inc.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

**APPEARS THIS WAY
ON ORIGINAL**

Study 3010

Name and Center	Address	# enrolled/ # completed (HCG administered**)	# not completed: # ND*/ # no HCG**/ # no ET***	SAEs
Devroey, Prof. Paul MD (Center 21) *(Note: the centers in this study are numbered from 21 to 27)*	Centre for Reproductive Medicine Academic Hospital Free University Brussels Laarbleeklan 101 B-1090 Brussels, Belgium	**49/44** CET: 33/31 BUS: 16/13	**11: 4/1/6** CET: 8: 2/0/6 BUS: 3: 2/1/0	2: CET 3: BUS
Brinsden, Prof. Peter MD (Center 22)	Bourn Hall Clinic Bourn Cambridge CB3 7TR, UK	**19/16** CET: 13/12 BUS: 6/4	**6: 1/2/3** CET: 4: 1/0/3 BUS: 2: 0/2/0	0
Lenton, Elizabeth MD (Center 23)	University of Sheffield Sheffield Fertility Centre 26 Glen Road Sheffield S7 IRA, UK	**23/19** CET: 16/12 BUS: 7/7	**6: 2/2/2** CET: 6: 2/2/2	0
Yates, Robert MD **Fleming, Prof. Richard Ph.D.** (Center 24)	University Department of Obstetrics and Gynaecology Royal Infirmary 10 Alexandra Parade Glasgow G31 2ER, UK	**48/38** CET: 32/28 BUS: 16/10	**18: 8/2/8** CET: 8: 3/1/4 BUS: 10: 5/1/4	1: BUS
Baird, Prof. David MD (Center 25)	University of Edinburgh Center for Reproductive Biology 37 Chalmers Street Edinburgh EH3 9EW, UK	**63/58** CET: 43/41 BUS: 20/17	**10: 4/1/5** CET: 6: 2/0/4 BUS: 4: 2/1°/1 °1 preg before COS	1: CET
Evers, Prof. Johannes MD (Center 26)	Department of Obstetrics and Gynaecology Academisch Ziekenhuis Maastricht P.O. Box 5800 NL-6202 AZ Maastricht, Netherlands	**31/25** CET: 21/18 BUS: 10/7	**8: 0/6/2** CET: 4: 0/3/1 BUS: 4: 0/3/1	0
Kahn, Prof. Jarl MD (Center 27)	Ciconia Fertility Clinic Frydendalsvej 5 DK-1809 Frederiksberg C., Denmark	**60/57** CET: 40/38 BUS: 20/19	**10: 0/3/7** CET: 5:0/2/3 BUS: 5: 0/1/4	0

Study 3020

Name and Center	Address	# enrolled/ # completed (HCG administered**)	# not completed: # ND*/ # no HCG**/ # no ET***	SAEs
Diedrich, Prof. Klaus MD (Center 1): Note: Due to deficiencies identified by an internal audit, data were excluded from efficacy analysis per July 15, 1999 FDA meeting	Klinik für Frauenheilkunde und Geburtshilfe Universitätskliniken Lübeck Rateburger Allee 160 D-23538 Lübeck, Germany	**45/43**	**2: 2/0/0**	2
Breckwoldt, Prof. Meinert MD (Center 2)	Klinik für Frauenheilkunde und Geburtshilfe Universitätskliniken Freiburg Hugstetter Strasse 55 D-79106 Freiburg, Germany	**11/11**	**2: 0/0/2**	0
van der Ven, Prof. Hans MD (Center 3)	Klinik für Frauenheilkunde und Geburtshilfe Universitätskliniken Bonn Sigmund-Freud-Strasse 25 D-53105 Bonn, Germany	**24/24**	**5: 0/0/5**	0
Siebzehnrübl, Ernst MD (Center 4)	Klinik f. Frauenheilkunde u. Geburtshilfe Abteilung für gynäkologische Endokrinologie und Reproduktionsmedizin Universitätsfrauenklinik Erlangen-Nürnberg D-91054 Erlangen, Germany	**11/11**	**2: 0/0/2**	0
Fischl, Prof. Franz MD (Center 5)	Abteilung für gynäkologische Endokrinologie und Sterilitätsbehandlung Universität für Frauenheilkunde Wien Währinger Gürtel 18-20 A-1090 Wien, Austria	**31/29**	**5: 1/1/3**	1
Urdl, Prof. Wolfgang MD (Center 6)	Klinische Abteilung für gynäkologische Endokrinologie Geburtshilflich-gynäkologische Universitätsklinik Graz Auenbruggerplatz 14 A-8036 Graz, Austria	**24/22**	**2: 2/0/0**	1
Zorn, Prof. Jean-René, MD (Center 7)	Service de Gynecologie-Obstetrique III Hôpital Cochin/Clinique Universitaire Baudelocque 123, Boulvard de Port-Royal F-75012 Paris, France	**27/24**	**3: 0/3/0**	0

Study 3020 (continued)

Name and Center	Address	# enrolled/ # completed (HCG administered**)	# not completed: # ND*/ # no HCG**/ # no ET***	SAEs
Tarlatzis, Prof. Basil MD (Center 8)	Infertility and IVF Centre Geniki Kliniki 2, Gravias Street GR-54645 Tessaloniki, Greece	**47/46**	**5: 0/1/4**	1
Cittadini, Prof. Ettore MD (Center 9) Site never started study	Clinica Ostetrica e Gynecologica University "R" Clinic of Palermo Via A. Giordano I-90127 Palermo, Italy	**NA**	**NA**	NA
Crosignani, Prof. Pier MD (Center 10)	Clinica Ostetrica e Gynecologica Universita degli Studi di Milano Via Commenda 12 I-20122 Milano, Italy	**24/23**	**8: 0/1/7**	0
Filicori, Prof. Marco MD (Center 11)	Clinica Ostetrica e Gynecologica Ospedale S. Orsolo/University of Bologna Reproductive Endocrinology Center Via Massarenti 13 I-40138, Bologna, Italy	**18/17**	**4: 1/1/2**	0
Ron-El, Prof. Raphael MD (Center 12)	IVF Unit Assaf Harofe Medical Center Affiliated with Sackler School of Medicine Zerefin 70300, Israel	**40/38**	**2: 0/2/0**	0
Barri, Prof. Pedro MD (Center 13)	Servicio de Medicina de la Reproducción Depto. de Obstetricia y Ginecologia Institut Universitari Dexeus Paseo Bonanova 89-91 E-08017 Barcelona, Spain	**19/16**	**3: 0/2/1**	0
von Düring, Vidar MD (Center 14)	Gynekologisk avdeling Røde Kors Klinikk / University of Trondheim Regionsykehuset i Trondheim N-7006 Trondheim, Norway	**31/26**	**5: 2/1/2**	0

Study 3030

Name and Center	Address	# enrolled/ # completed (HCG administered**)	# not completed: # ND*/ # no HCG**/ # no ET***	SAEs
Frydman, Prof. René MD (Center 1)	Hôpital Antoine Béclère 157, Rue de la Porte Trivaux F-92140 Clamart, France	**34/30** CET: 26/23 TRI: 08/7	**7: 4/0/3** CET: 4: 3/0/1 TRI: 3: 1/0/2	0
Belaïsch-Allart, Prof. Joelle MD (Center 2)	Hôpital de Sèvres Centre Hospitalier Jean Rostand 141, Grande Rue F-92310 Sèvres, France	**27/23** CET: 20/17 TRI: 7/6	**4: 4/0/0** CET: 3: 3/0/0 TRI: 1: 1/0/0	CET: 1 TRI: 1
Dellenbach, Prof. Pierre MD (Center 3)	Centre Médico-chirugical et obstétrical 19, Rue Louis Pasteur F-67300 Schiltigheim, France	**18/15** CET: 13/10 TRI: 5/5	**3: 3/0/0** CET: 3: 3/0/0	CET: 1 TRI: 1
Emperaire, Jean-Claude MD (Center 4)	35, Rue Turenne F-33000 Bordeaux, France	**26/23** CET: 20/19 TRI: 6/4	**3: 1/2/0** CET: 1: 1/0/0 TRI: 2: 0/2/0	0
Hedon, Prof. Bernard MD (Center 5)	Fédération des Services de Gynécologie Obstétrique Hôpital Arnaud de Villeneuve 371, Avenue Doyen Gaston Giraud F-34295 Montpellier Cedex, France	**23/21** CET: 17/15 TRI: 6/6	**4: 1/1/2** CET: 3: 1/1/1 TRI: 1: 0/0/1	CET: 1
Nicollet, Bernard MD (Center 6)	Institut Rhône-alpin 1, Rue Laborde F-69500 Bron, France	**12/12** CET: 9/9 TRI: 3/3	**1: 0/0/1** TRI: 1: 0/0/1	0
Salat-Baroux, Prof. Jaques MD (Center 7)	Hôpital Tenon 4, Rue de la Chine F-75970 Paris, France	**23/19** CET: 17/16 TRI: 6/3	**3: 3/1/0** CET: 1: 0/1/0 TRI: 3: 3/0/0	0
Zorn, Prof. Jean-René, MD (Center 8)	Service de Gynecologie-Obstetrique III Hôpital Cochin/Clinique Universitaire Baudelocque 123, Boulvard de Port-Royal F-75014 Paris, France	**6/5** CET: 4/3 TRI: 2/2	**1: 0/1/0** CET: 1: 0/1/0	0

* ND: no drug given (in 3010 & 3030, this means either no Cetrorelix, Buserelin or Triptorelin; in 3020, this means either Cetrorelix or hMG)

** no HCG given: drop out according to study protocol (primary parameter)

*** no ET: HCG administered, but oocyte pick up or ART failed, to be evaluated as drop out during follow up (post treatment)

No patient discontinued from any study due to intolerability

Abbreviations: SAE = serious adverse event; CET = Cetrorelix; BUS = Buserelin; TRI = Triptorelin; hMG = Human Menopausal Gonadotropin; HCG = human chorionic gonadotropin

FAX

ORIGINAL

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

ORIG AMENDMENT
BC

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 Árny, Senior Regulatory Associate, at ext. 403.

Sincerely,

Brian A. Green

Brian A. Green

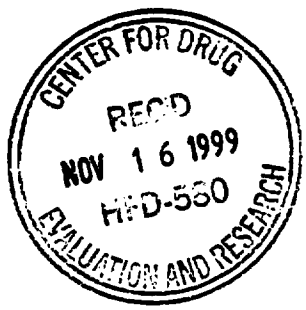
NEW CORRESP
N L

November 15, 1999

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

Telephone 978.851.5981
Telefax 978.851.7346

Lisa Rarick, MD, Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Office of Drug Evaluation II, CDER, FDA
Room 17B-45
5600 Fishers Lane
Rockville, MD 20852



Re: CETROTIDE™ (cetrorelix acetate for injection)
NDA 21-197
REQUEST FOR WAIVER OF PEDIATRIC ASSESSMENT

Dear Dr. Rarick:

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.

Reference is also made to the Federal Register notice dated December 2, 1998 (63 FR 66631) that notified the pharmaceutical industry that, after April 1, 1999, all New Drug Applications were required to contain studies of the new drug in the pediatric population or the sponsor's plans for pediatric development of the new drug.

In accordance with 21 CFR §314.55(c)(2), ASTA Medica, Inc. hereby respectfully requests a full waiver of the requirements of 21 CFR §314.55(a) to assess the safety and effectiveness of CETROTIDE™ for the claimed indication above in the entire pediatric population.

As required under Part 314.55(c)(2)(i), ASTA Medica certifies that CETROTIDE™ "does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a substantial number of pediatric patients" for the prevention of premature ovulation in patients undergoing controlled ovarian stimulation.

As stated above, the claimed indication for CETROTIDE™ is the prevention of premature ovulation in patients undergoing controlled ovarian stimulation. Controlled ovarian stimulation is used as a first step in various assisted reproduction techniques for the female partner of infertile couples. Infertility is generally defined as the inability to achieve pregnancy after a minimum of one year of unprotected intercourse. Patients seeking medical assistance after 12 months of attempting to get pregnant would then undergo a series of examinations to determine the cause of infertility.

The time required for examinations, discussion of treatment options, and implementation of a treatment could range from 3-6 months. This results in a total timeframe of 15-18 months from the initial attempts at pregnancy. ASTA Medica believes that it is very unlikely that any patients under the age of 16 years old would require CETROTIDE™ therapy.

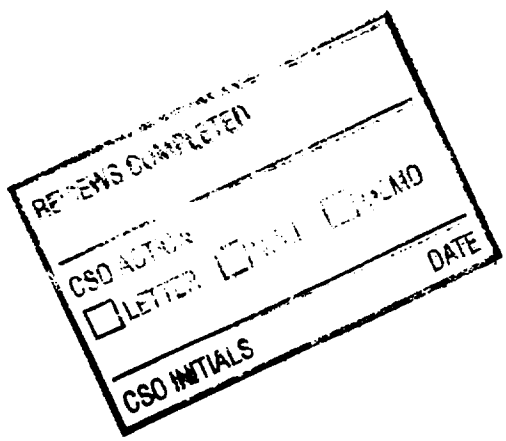
In conclusion, because NDA 21-197 provides for the use of CETROTIDE™ as an adjunctive therapy for use in assisted reproduction techniques, it is not likely to be used in the pediatric population to any extent. In addition, CETROTIDE™ does not represent a meaningful therapeutic benefit for pediatric patients, for the claimed indication of prevention of premature ovulation in patients undergoing controlled ovarian stimulation. Therefore, we feel we have met the requirements for a waiver of pediatric assessment of CETROTIDE™.

If you have any questions or require any additional information, please feel free to contact me at (978) 851-5981, ext. 220.

Sincerely,

Brian A. Green

Brian A. Green
Senior Regulatory Affairs Associate
ASTA Medica, Inc.



APPEARS THIS WAY
ON ORIGINAL

ASTA MEDICA

October 28, 1999

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

Telephone 978.851.5981
Telefax 978.851.7346

Lisa Rarick, MD, Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II, CDER, FDA
HFD-580
5600 Fishers Lane
Rockville, MD 20852

Re: **CETROTIDE™ (cetrorelix acetate for injection)**
NDA #21-197
Initial NDA Submission

Dear Dr. Rarick:

In accordance with Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act and 21 CFR §314.50, we are submitting 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.

Included in this NDA are three Phase III studies in adults. These studies were conducted as part of a European clinical program. Two studies were conducted with the 0.25 mg multiple-dosing regimen (Studies 3010 and 3020) and one with the 3.0 mg single-dosing regimen (Study 3030). Active control drugs were used in two of the studies, since conducting placebo-controlled studies for the proposed indication could not be ethically justified. Study 3010 used buserelin (BUS) and single-dose Study 3030 used triptorelin (TRI). Although BUS and TRI are approved in some European countries for the proposed indication, these drugs have not been approved in the United States and, therefore, the data from these control groups are not acceptable by the FDA for analysis of the efficacy or safety of CET.

Reference is made to a meeting held on October 30, 1996 between ASTA Medica and the Division to discuss the US clinical development of cetrorelix in this indication. The FDA agreed that the European data were acceptable as the basis of an NDA submission, if these data were presented together with a suitable historical control consisting of women undergoing ovarian stimulation without concomitant LHRH-agonist or LHRH-antagonist therapy.

ASTA Medica obtained the required historical control data from the National In Vitro Fertilization-Embryo Transfer (IVF-ET) Registry published and prepared by the American Fertility Society (AFS) and the Society of Assisted Reproductive Technology (SART). The historical control group included subjects who received ovarian stimulation without LHRH-agonist or LHRH-antagonist therapy.

Seven Phase II efficacy studies were also conducted. These include four Proof of Concept Studies (0008, 0009b, 0012 and IC93005), two Dose Finding Studies (Studies 2986 and 2997), and one Exploratory Study using two different gonadotropins (recFSH or HMG) for ovarian stimulation (Study 3097).

In the preparation of our NDA submission, audits were conducted at the majority of centers participating in the adequate and well-controlled studies (3 non-US Phase III studies). The performed QA audits revealed that in one center of Study 3020, the conduct of the study showed evidence of deviations from the regulations in several areas. These issues were in a July 15, 1999 meeting with the Division. A copy of the meeting minutes is included on page 20 of Volumes 73 of the Clinical and 132 of the Statistical Data Sections of this NDA.

The Archival Copy of this NDA consists of 162 volumes. Volume 1 includes a detailed Index (including the Tables of Contents for each of the clinical reports) as well as the Application Summary.

The Chemistry, Manufacturing and Controls data are included in Volumes 2-18. The Sterility Validation portion for microbiology review is provided in Volume 19. Nonclinical Pharmacology and Toxicology Data are in Volumes 20-42. The Human Pharmacokinetics and Bioavailability Section is contained in Volumes 43-72. The Clinical and Statistical Data Sections are provided in Volumes 73-131 and Volumes 132-161, respectively. Case Report Forms for those subjects who dropped out of the studies due to adverse events are provided in Volume 162 (only in the archival copy of this application).

Together with the paper copy of this NDA, we are also providing 2 CDs of the text and tables of the clinical reports for the dose finding studies (2986 and 2997), the Phase III studies (3010, 3020, 3030), the ISS, ISE, and SAS data sets. These discs are being provided as reviewers' aids together with four additional desk copies of Volume 1.1 (Application Summary Volume). Two additional CDs containing the Application Summary and labeling are also provided.

If you have any questions or require any additional information concerning the information in this NDA, please feel free to contact me or Brian A. Green, Senior Regulatory Affairs Associate, at (978) 851-5981, ext. 220.

Sincerely,

Colin Stewart
President and CEO
ASTA Medica, Inc.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MAY 02 2000

NDA 21-197

DISCIPLINE REVIEW LETTER

ASTA Medica, Inc.
Attention: Colin Stewart
President and CEO
890 East Street
Tewksbury, MA 01876-1496

Dear Mr. Stewart:

Please refer to your October 28, 1999 new drug application for Cetrotide™ (cetrorelix acetate for injection).

Our review of the Microbiology section (microbiology issues concerning sterility assurance) of your submission is complete, and we have identified the following comments and information requests:

1. Regarding bacterial retention validation of the intended sterilizing filter:

   a. Please compare the filtration parameters (pressure, flow rate, etc.) used during validation testing to process parameters.

   b. The integrity (forward flow) test values demonstrated by the three test filters were approximately 1/6 of the maximum recommended forward flow. Testing filters in this range does not validate the use of filters at or near the manufacturer's integrity test value.

2. Regarding the moist heat sterilization of the equipment:

   a. Please provide the diagrams and/or descriptions of the equipment load used for validation. Please include thermocouple and biological indicator positions within the load. If applicable, a rationale for "worst case" locations or equipment should be provided.

   b. It is unclear from ~~the~~ descriptions provided if only one load configuration applicable to the manufacture of the subject drug is sterilized using the [redacted] If this load configuration contains all the equipment used to fill the drug product, it should be stated. If not, other equipment loads should be described and/or diagrammed, indicating the positions of monitoring thermocouples and biological indicators. Validation data for alternate loading patterns should also be included.

3. Regarding the dry heat sterilization of equipment:

   a. Please define the term [redacted] used on page 154 of the submission ("Validation Report for the validation of the sterilization of equipment...' [redacted]

   b. Please provide load diagrams and descriptions of equipment indicating thermocouple and biological indicator positions used in dry heat sterilizer validation studies.

   c. If more than one load configuration is sterilized in these dry heat units, each load configuration should be described and validation data for those loads provided. Alternatively, data obtained using the "worst case load" may be provided along with a rationale for the choice of the "worst case load" may be provided along with a rationale for the choice of the "worst case" loading pattern.

4. The descriptions of the environmental microbiological monitoring program are too abbreviated. Please include the frequency of monitoring, type of monitoring, sites monitored, alert and action level specifications, and precise descriptions of the actions taken when specifications are exceeded.

   a. Microbiological Methods

      Please describe the microbiological materials and methods used in the environmental monitoring program. Methods may include sample collection, transport, neutralization of sanitizers, incubation, and calculation of results. Please address, including specifications, the following sources of contamination and their monitoring:

      (1) Airborn microorganisms

      (2) Microorganisms on inanimate surfaces

      (3) Microorganisms on personnel

      (4) Water systems

      (5) Product component bioburden

   b. Yeasts, Molds, and Anaerobic Microorganisms

      Please provide a description of periodic or routine monitoring methods used for yeast, molds, and anaerobes.

   d. Exceeded Limits

      Please provide a description of the actions taken when specifications are exceeded.

5. Regarding container/closure integrity testing:

   a. The methods used to remove the stoppers and rinse the test vials following immersion are unclear from the descriptions provided. Please describe these methods in greater detail, paying special attention to the rinsing of the stopper – glass interfaces.

   b. Please provide data demonstrating the level of bacteriostatic and fungistatic activity of the reconstituted product solution.

   c. Please provide positive control results. This should include the methods used to provided a breech in the integrity of the container/closure system.

   d. Regarding [redacted] we have found that the DMF is not adequate to support your application, and a separate information request letter has been sent out to the DMF holder.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, call Jeanine Best, MSN, RN, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

/S/

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader, for the
Division of Reproductive and Urologic Drug Products,
(HFD-580)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

NDA 21-197

NOV 03 1999

ASTA Medica, Inc.
Attention: Colin Stewart
President and CEO
890 East Street
Tewksbury, MA 01876-1496

Dear Mr. Stewart:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: CETROTIDE (cetrorelix acetate for injection) 0.25 mg and 3 mg

Therapeutic Classification: Standard (S)

Date of Application: October 28, 1999

Date of Receipt: October 29, 1999

Our Reference Number: NDA 21-197

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on December 28, 1999 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be August 29, 2000 and the secondary user fee goal date will be October 29, 2000.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within 120 days of receipt of your pediatric drug development plan, we will notify you of the pediatric studies that are required under section 21 CFR 314.55.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov.cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will proceed with the pediatric drug development plan that you submit and notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, contact Jeanine Best, MSN, RN, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

/S/ 11/2/99

Terri Rumble
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Archival NDA 21-197
HFD-580/Div. Files
HFD-580/JBest
HFD-580/Reviewers and Team Leaders
DISTRICT OFFICE

Drafted by: JAB/November 2, 1999
Initialed by: Rumble
final: JAB/November 2, 1999
filename: N21197ACKL1199.doc

ACKNOWLEDGEMENT (AC)

Number of Pages Redacted 14

❖❖❖

Confidential,
Commercial Information

MEETING MINUTES

Date: July 15, 1999 **Time:** 10:30 - 11:20 AM **Location:** Parklawn; Chesapeake Room

IND: [redacted] **Drug Name:** Cetrorelix

Indication: Controlled ovarian stimulation for ART

Type of Meeting: Pre-NDA

External Participant: ASTA Medica, Inc.

Meeting Chair: Dr. Lisa Rarick **External Participant Lead:** Dr. Reithmuller-Winzen

Meeting Recorder: Ms. Diane Moore

FDA Attendees:
Lisa Rarick, M.D. - Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580) (via telephone)
Shelley Slaughter, M.D., Ph.D. - Medical Officer, DRUDP (HFD-580)
Ridgely Bennett, M.D., M.P.H. - Medical Officer, DRUDP (HFD-580)
Diane Moore - Project Manager, DRUDP (HFD-580)
David Hoberman – Statistician – @DRUDP (HFD-580)
DJ Chatterjee, Ph.D. – Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)
Gurston Turner, Ph.D. – Office of Compliance, Division of Scientific Investigations (OC, DSI) (HFD-45)

External Constituents:
Aileen Ryan – Regulatory Affairs, ASTA Medica, Inc., Tewksbury, MA
I. Amy, M.D. – Regulatory Affairs, ASTA Medica, Inc. Tewksbury, MA
H. Riethmüller-Winzen, M.D. – Medical Research, ASTA Medica AG, Frankfurt, Germany
K. Junge, Ph.D. – Biometrics, ASTA Medica AG, Frankfurt, Germany
S. Geussenhainer, Ph.D. – Quality Assurance, ASTA Medica AG, Frankfurt, Germany
M. Erspamer - Consultant

Meeting Objectives:
To discuss the findings at the Lübeck manufacturing site and what the sponsor has done to correct the deficiencies found at that site. The Lübeck site is one of the sites included in the pivotal trial for Cetrorelix (see meeting package dated June 9, 1999).

Discussion Points:

- the sponsor previously proposed to submit the recalculated data from the Lubeck site as an appendix but is now proposing to write a totally new report retrospectively putting in new data
- study monitors reported problems at the Lubeck site prior to the internal audit; examples were disorganization of patient files, lack of study coordinator and over-worked staff; the sponsor hired a study coordinator, trained personnel and organized patient files
- all other study sites were acceptable in internal audits
- additional parameters were taken at the Lubeck site that were not taken at other sites such as luteal phase support after embryo transfer

- the data is not much different when the Lubeck site is included or excluded
- all studies were performed in Europe

Decisions reached:

Question 1: As a result of the October 1998 audit of the Lübeck site, a 100% reaudit was performed and all transcription errors were entered into the database and new tables and listings produced. Please confirm that our proposal for including these revised data as an appendix to the Clinical Report for 3020 is acceptable.

Answer:

- FDA is concerned about adding data retrospectively
- the data from the Lübeck site should not be included in the efficacy analysis for Cetrorelix
- because the NDA can stand without the Lubeck data, the report could be done without the data or it could be done both with and without the data from the Lubeck site

Question 2: The ISS tables and listings will include the updated data but the ISS will not specifically site any of the revised data. Please confirm that this approach is acceptable.

Answer:

- the data should be included in the text; narrative should not differ from the tables and listings and should include all safety data
- although the ISS database may differ from study reports, the Lübeck safety data could be retained in the ISS
- a discussion of the Lubeck site should be reflected in the study report or the ISS, not both

Question 3: In the ISE we have proposed to include two analyses versus the historical control; one including the Lübeck center and one excluding the Lübeck center. Please confirm that this is acceptable.

Answer:

- Yes

Question 4: The analysis, which we will perform without the Lübeck center, will be the efficacy parameter used for comparison to the historical control (oocyte retrieval/puncture done) only. We are not planning to conduct sensitivity analyses with and without the Lübeck center for any other parameters (e.g. pregnancy, deliveries etc.) Please confirm that this is acceptable.

- there is no data base for historical control for premature LH surge and historical comparisons are dissimilar in certain categories

Answer:

- primary parameters can be included in the analysis report
- the sponsor noted that the number of oocytes will be the only endpoint compared to a historical control

FDA questions

- Was Dr. Dietrick's site included in other studies:
  - **answer**: not in the dose finding study, only the multiple-dose study and 2 pilot studies in 19 patients
- were Phase 2 studies performed at Lübeck?
  - **answer:** one half of the subjects in the PK studies were from Lubeck, the Lübeck site was used in two Phase 2 pilot studies, but not the dose finding studies; plasma sampling was included at the

Meeting Minutes – July 15, 1999

Lübeck site

- a list of investigators and sites for the Phase 1, 2 and 3 studies should be provided
- target date for NDA submission is September, 1999

Action Items:

	Responsible Person:	**Due Date:**
• **Item**		
• provide list of investigators and sites for and Phase 1, 2 and 3 studies	ASTA Medica	prior to NDA Phase 1, 2 submission
• minutes to sponsor	Ms. Moore	1 month

/S/ 9/13/99
Signature, minutes preparer

/S/ 9/16/99
Concurrence, Chair

drafted: dm/08.14.99/i33756MM71999.doc

Concurrences:
RBennett, DChatterjee 08.16.99/LRarick 09.10.99

Concurrence not received from:
SSlaughter/DHoberman/GTurner

cc:
NDA Arch:
HFD-580
HFD-580/LRarick/MMann/SSlaughter/RBennett/MRhee/LKammerman/DMoore/FDeguia
HFD-580/TRumble/SMadani/AParekh/DHoberman/DChatterjee
HFD-45/GTurner

APPEARS THIS WAY
ON ORIGINAL

MEETING MINUTES

Date: October 30, 1997 **Time:** 1:15 - 2:45 PM **Location:** Pkln: Conf. Rm B

IND: —— **Drug Name:** Cetrorelix

External Participant: ASTA Medica, Inc. **External Participant Lead:** A. Ryan

Type of Meeting: Guidance

Meeting Chair: Lisa Rarick, M.D.

Meeting Recorder: Alvis Dunson

FDA Attendees:

Lisa Rarick, M.D. - Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Heidi Jolson, M.D., M.P.H. - Deputy Director, DRUDP (HFD-580)
Ridgely Bennett, M.D., M.P.H. - Medical Officer, DRUDP (HFD-580)
Lisa Kammerman, Ph.D. - Statistical Team Leader, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
Vanketeswar Jarugula, Ph.D. - Pharmacokinetics Reviewer, DPE II @ DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC) @ DRUDP (HFD-580)
Krishan Raheja, Ph.D., D.V.M. - Pharmacologist, DRUDP (HFD-580)
Alvis Dunson - Project Manager, DRUDP (HFD-580)

External Constituents:

A. Ryan - Regulatory Affairs
R. Venhaus, M.D. - Medical Affairs
J. Rawert, Ph.D. - Project Management
G. Reuschenbach, Ph.D. - Regulatory Affairs
H. Riethmuller-Winzen, M.D. - Medical Affairs
H. Nowak, Ph.D. - Biometrics
J. Engel, Ph.D. - Biometrics
M. Scharf, Ph.D. - Pharmaceutical Development
W. Jahn, Ph.D. - Preclinical Research

Meeting Objectives:

To discuss the U.S. clinical development of Cetrorelix for the prevention of premature ovulation in patients undergoing fertilization treatments.

Discussion Points:

The sponsor proposed the following questions for Division comment:

Q1: We have conducted Phase 2 and 3 clinical studies using multiple doses of 0.25 mg Cetrorelix and single doses of 3 mg Cetrorelix. Three Phase III studies were conducted; two with the 0.25 mg multiple dosing regimen and one with the 3 mg single dose regimen. In two of the studies active controls were used. These are approved products in certain countries of Europe for this indication, but have not been approved in the US. The first study, Protocol D-20761-3010 (Vol. 2; Tab 7) is an open randomized multi-center controlled study where intra nasally administered buserelin is used as the control. The second study, Protocol D-20761-3020 (Vol. 2; Tab 8) is an open uncontrolled multi-center study. **Are the study designs and the proposed methods of analysis adequate for FDA to accept these studies as adequate and well controlled studies? Are there any additional issues which need to be addressed?**

A1: A historical argument should be made for the use of Cetrorelix in controlling premature LH surge since the active comparitors used in the studies are not approved. Special attention should be paid to the age groups used in the studies when using the registry data for canceled cycles because the study is enrolling women below the age of 40. Provide confidence intervals on the differences in rates of canceled cycles between the Cetrorelix group and the historical reference. Propose what will be the clinically significant difference in rates of canceled cycles between the Cetrorelix group and the historical reference. Any additional safety data on longer term use should also be submitted.

Q2: The 3 mg single dose of Cetrorelix was utilized in Protocol D-20761-3030 (Vol 2; Tab 9) which is an open, randomized, multi-center controlled study with triptorelin as the control. **Will this study be sufficient to support the approval of the 3 mg single dosing schedule?**

A2: A determination of approvability cannot be made until the NDA has been deemed acceptable for filing by the Division and reviewed. The application is required to contain reports of all investigations of the drug product sponsored by the applicant, and all other information about the drug pertinent to an evaluation of the application. FDA has guidelines on the format and content of applications to assist applicants in their preparation. It is likely that this study along with all the other studies performed, will be sufficient to support the filability of the 3 mg single dosing regimen.

Q3: The ultimate aim of the treatment is to obtain a controlled ovulation and the retrieval of at least one mature (metaphase II) oocyte suitable for assisted reproduction techniques (ART). Cetrorelix as an LHRH-antagonist is expected to prevent a premature ovulation triggered by premature LH surges (LH $\geq$ 10 IU/l and Progesterone $\geq$ 1 ng/ml serum). **Patients are categorized as responders based on whether the HCG day is reached. Is this an acceptable endpoint for these studies?**

A3: The primary endpoint is acceptable provided that clinical data on pregnancy outcomes is also provided and supports the efficacy of this product. Outcome data should include the following:

- clinical pregnancy per initiated cycle
- clinical pregnancy rate per embryo transfer
- ongoing pregnancy rate per cycle initiated
- live birth rate per cycle initiated
- live birth rate per embryo transfer

Propose how evidence of satisfactory clinical outcome will be factored into the analysis.

Q4: The clinical program performed in Europe included women from ages 18-39 and most likely will not include the racial distribution which is characteristic of the US population. **Will this be a problem in accepting these data as primary evidence of efficacy?**

A4: Because there appears to be no differences in response to infertility treatments between races, this does not present a problem.

Q5: **Is the clinical program sufficient and if not what additional studies/data will be required?**

A5: The clinical program appears sufficient but further clarification is needed on the use of historical data and reassurance on how secondary endpoints will be analyzed.

Q6:

A6:

Q7: **Are any additional preclinical studies required for approval of Cetrorelix for use in controlled ovulation induction?**

A7: Required reprotoxiticy studies have been conducted but complete results need to be submitted, reviewed and evaluated.

Q8: During the clinical program, ampules of water for injection were provided for reconstitution of the Cetrorelix. We are in the process of evaluating a pre-filled syringe to be used for this purpose. The syringe will be filled with Water for Injection which will meet the following specifications at the end of its shelf-life. **We would like confirmation from the Division that this approach is acceptable.**

A8: The following CMC data should be submitted:

- the specification should meet the USP requirements for Sterile Water for Injection, pH, and particulate matter
- the label should indicate "Sterile Water for Injection, USP"
- stability data should be submitted for review.

Other

Biopharmaceutics

- submit the following PK data as part of the NDA submission:
  - single dose (3.0 mg) and multiple dose (0.25 mg) PK data
  - dose proportionality data
  - effect of concentration of the injection on the PK of the drug

Unresolved Issues: None

Action Items:

	Item:	**Responsible Person:**	**Due Date:**
♦	submission of information requested in the above responses to questions	ASTA Medica, Inc.	?
♦	schedule T-con between sponsor and Clinical/Biometrics reviewers following review of amended analysis plan	Alvis Dunson	?

/S/ 11/18/97
Signature, minutes preparer

/S/ 11/18/97
Concurrence, Chair

drafted: ADunson/11.3.97/i46333im

cc:
NDA Arch:
HFD-580
HFD-580/JMercier/Attendees
HFD-580/ADunson/11.3.97

Concurrences:
RBennett, LPauls, Hjolson, MRhee11.4.97/KRaheja11.5.97/LKammerman11.6.97/
VJarugula11.10.97

APPEARS THIS WAY
ON ORIGINAL

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

There was no Advisory Committee held for this drug product.

MEMO

45 Day Filing Meeting Checklist
Project Management

ITEM NDA 21-197 Cetrotide ™ (cetrorelix acetate for injection)	YES	NO	COMMENT
1) Do any of the following apply to this application (i.e., if yes, the application **MUST BE REFUSED TO FILE** under 314.100(e) and there is no filing over protest):		X	
a. Is the drug product already covered by an approved application?		X	
b. Does the submission purport to be an abbreviated application under 314.55; however, the drug product is not one for which FDA has made a finding that an abbreviated application is acceptable under 314.559b)?		X	
c. Is the drug product subject to licensing by FDA under the Public Service Act and Subchapter F of Chapter I of Title 21 of the CFR?		X	
2) Do any of the following apply to this application (i.e., if NO, the application **MAY BE REFUSED TO FILE** under 314.100(d) and there is the potential for filing over protest):	X		
a. Does the application contain a completed application form as required under 314.50 or 314.55?	X		
b. On its face, does the application contain the sections of an application required by regulation and Center guidelines?	X		

ITEM	YES	NO	COMMENT
c. Has the applicant submitted a complete environmental assessment, which addresses each of the items, specified in the applicable format under 25.31 or has the applicant submitted evidence to establish that the product is subject to categorical exclusion under 25.24 of the CFR?	X		
d. On its face, is the NDA formatted in compliance with Center guidelines including integrated efficacy and safety summaries?	X		
e. Is the NDA indexed and paginated?	X		
f. On its face, is the NDA legible?	X		
g. Has the applicant submitted all required copies of the submission and various sections of the submission?	X		
h. Has the sponsor submitted all special Studies/data requested by the Division during presubmission Discussion with the sponsor?	X		
i. Does the application contain a statement that all nonclinical laboratory studies were conducted in compliance with the requirements set forth in Part 58 or a statement why a study was not conducted in compliance with those requirements?	X		
j. If required, has the applicant submitted carcinogenicity studies?			NA

ITEM	YES	NO	COMMENT
k. On its face, does the application contain at least two adequate and well-controlled clinical trials?	X		
l. Does the application contain a statement that all clinical trials were conducted in accord with the IRB/Declaration of Helsinki provisions of the CFR?	X		
m. Have all articles/study reports been submitted either in English or translated into English?	X		
n. Has the applicant submitted draft labeling in compliance with 210.56 and 210.57 of the CFR?	X		
3) From a project management perspective, is this NDA fileable? If "no", please state why it is not.	X		

/S/ MSN RN 12/15/99

Regulatory Project Manager

/S/ 12/16/99

Chief, Project Management Staff

cc:
Original NDA
HFD-580/DivFile
HFD-580/Best

MEMORANDUM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Date: March 31, 2000

TO: Roy Blay, Ph.D., Senior Regulatory Reviewer (HFD-46)

FROM: Lana L. Pauls, M.P.H., Associate Director, Division of Reproductive and Urologic Drug Products HFD-580

SUBJECT: Request for additional Clinical Inspection as per conversation on 3/20/00 for NDA 21-197

In support of the above mentioned NDA for Cetrotide™ (cetrorelix acetate for injection) 0.25 and 3 mg, the sponsor, ASTA Medica, Inc., submitted the results of the following pivotal protocol for the indication of prevention of premature ovulation in patients undergoing controlled ovarian stimulation:

Pivotal Protocol #	Investigator's Name/Address
3030 Site #1	Professor Rene Frydman Dr. Francois Olivennes Hospital Antoine Beclere 184 rue du Faubourg Saint-Antoine 92140 CLAMART/France

We are requesting this additional site for investigation because:

1. Pivotal Trial #3030 involves the single 3 mg dose.
3. The data from this site appears better on paper when compared to other sites.

The reviewing Medical Officer for this application is Jerry Willett, M.D., phone

The Medical Team Leader is Shelley Slaughter, M.D., Ph.D., phone

The responsible Project Manager is Jeanine Best, M.S.N., R.N., phone 7-4268.

The user fee goal date is August 29, 20000.

The Division's action goal date is July 18, 2000.

cc: Arch. NDA 21-197
HFD-580Div File
HFD-344/Div liaison
HFD-580/Slaughter/Willett
HFD-580/Best

N21197DSIMemo0300.doc

APPEARS THIS WAY
ON ORIGINAL

best

MEMORANDUM

Date: January 7, 2000

To: Roy Blay, GCPB Reviewer/HFD-46 LP 1/7/00

From: Lana Pauls, M.P.H.., Associate Director, Review Division /HFD-580

Subject: **Request for Clinical Inspections**
NDA 21-197
Sponsor Name: Asta Medica, Inc.
Drug Trade Name and Generic Name: Cetrotide™ (cetrorelix acetate for Injection) 0.25 and 3 mg (a NME).

Section A: Protocol/Site Identification

As discussed with you, the following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority. The sponsor is the monitor of these sites.

Indication: Prevention of premature ovulation in patients undergoing controlled ovarian stimulation

Pivotal Protocol #	Investigator's Name/Address
C-25-3010	Professor D. Baird, M.D. Center for Reproductive Biology University of Edinburgh Edinburgh, United Kingdom
C-24-3010	R.W.S. Yates, M.D. Professor R. Flemming, Ph.D. E. Louis, M.D. University Department OB-GYN Royal Infirmary Glasgow, United Kingdom

International inspection requests (Section B) or requests for five or more inspections (Section C) require sign-off by the ORM Division Director and forwarding through the Director, DSI.

Section B (optional): International Inspections

We have requested inspections because (please check appropriate statements):

____ There are insufficient domestic data; or

_X__ Only foreign data are submitted to support an application; or

____ Domestic and foreign data show conflicting results pertinent to decision-making; or

____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations.

____ Other_____

Section D: Goal Date for Completion

We request that the inspections be performed and the Inspection Summary Results be provided by July 18, 2000. We intend to issue an action letter on this application by August 29, 2000

Should you require any additional information, please contact Jeanine Best, M.S.N., R.N., Regulatory Project Manager, phone 7-4268.

APPEARS THIS WAY
ON ORIGINAL

Distribution: /NDA 21-197
HFD-580/Division File
HFD-580/Project Manager/Best
HFD-46/GCPB Reviewer/Blay
HFD-45/Program Management Staff

MEMORANDUM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: December 13, 1999

TO: Roy Blay, Senior Regulatory Reviewer (HFD-46)

LLP 12/13/99

FROM: Lana L. Pauls, M.P.H., Associate Director, Division of Reproductive and Urologic Drug Products HFD-580

SUBJECT: Request for Clinical Inspections for NDA 21-197

In support of the above mentioned NDA for Cetrotide™ (cetrorelix acetate for injection) 0.25 and 3 mg, the sponsor, ASTA Medica, Inc., submitted the results of the following pivotal protocols for the indication of prevention of premature ovulation in patients undergoing controlled ovarian stimulation:

Pivotal Protocol #	Investigator's Name/Address
C-25-3010	Professor D. Baird, M.D. Center for Reproductive Biology University of Edinburgh Edinburgh, United Kingdom
C-5-3030	Professor Bernard Hedon Federation des Services de Gynecologie Obstetrique Hospital Arnaud de Villeneuve 371, Avenue Doyen Gaston Giraud 34295 Montpellier Cedex, France

We have discussed this application with Roy Blay and, as a result, identified the above protocols/sites for inspection.

The reviewing Medical Officer for this application is Jerry Willett, M.D., phone ——

The responsible Project Manager is Jeanine Best, M.S.N., R.N., phone 7-4268.

The user fee goal date is August 29, 20000.

The Division's action goal date is July 18, 2000.

cc: Arch. NDA 21-197
HFD-580Div File
HFD-344/Div liaison
HFD-580/Willett
HFD-580/Best

N21197DSIMemo1299.doc

APPEARS THIS WAY
ON ORIGINAL

Number of Pages Redacted 2

❖❖❖

Confidential,
Commercial Information

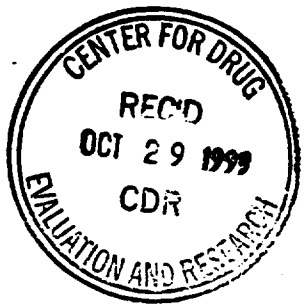
OK Lana 12/6/99

October 28, 1999

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

Telephone 978.851.5981
Telefax 978.851.7346

Lisa Rarick, MD, Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II, CDER, FDA
HFD-580
5600 Fishers Lane
Rockville, MD 20852



Re: **CETROTIDE™ (cetrorelix acetate for injection)**
NDA #21-197
Initial NDA Submission

Dear Dr. Rarick:

In accordance with Section 505(b)(1) of the Federal Food, Drug and Cosmetic Act and 21 CFR §314.50, we are submitting 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.

Included in this NDA are three Phase III studies in adults. These studies were conducted as part of a European clinical program. Two studies were conducted with the 0.25 mg multiple-dosing regimen (Studies 3010 and 3020) and one with the 3.0 mg single-dosing regimen (Study 3030). Active control drugs were used in two of the studies, since conducting placebo-controlled studies for the proposed indication could not be ethically justified. Study 3010 used buserelin (BUS) and single-dose Study 3030 used triptorelin (TRI). Although BUS and TRI are approved in some European countries for the proposed indication, these drugs have not been approved in the United States and, therefore, the data from these control groups are not acceptable by the FDA for analysis of the efficacy or safety of CET.

Reference is made to a meeting held on October 30, 1996 between ASTA Medica and the Division to discuss the US clinical development of cetrorelix in this indication. The FDA agreed that the European data were acceptable as the basis of an NDA submission, if these data were presented together with a suitable historical control consisting of women undergoing ovarian stimulation without concomitant LHRH-agonist or LHRH-antagonist therapy.

ASTA Medica obtained the required historical control data from the National In Vitro Fertilization-Embryo Transfer (IVF-ET) Registry published and prepared by the American Fertility Society (AFS) and the Society of Assisted Reproductive Technology (SART). The historical control group included subjects who received ovarian stimulation without LHRH-agonist or LHRH-antagonist therapy.

Seven Phase II efficacy studies were also conducted. These include four Proof of Concept Studies (0008, 0009b, 0012 and IC93005), two Dose Finding Studies (Studies 2986 and 2997), and one Exploratory Study using two different gonadotropins (recFSH or HMG) for ovarian stimulation (Study 3097).

In the preparation of our NDA submission, audits were conducted at the majority of centers participating in the adequate and well-controlled studies (3 non-US Phase III studies). The performed QA audits revealed that in one center of Study 3020, the conduct of the study showed evidence of deviations from the regulations in several areas. These issues were in a July 15, 1999 meeting with the Division. A copy of the meeting minutes is included on page 20 of Volumes 73 of the Clinical and 132 of the Statistical Data Sections of this NDA.

The Archival Copy of this NDA consists of 162 volumes. Volume 1 includes a detailed Index (including the Tables of Contents for each of the clinical reports) as well as the Application Summary.

The Chemistry, Manufacturing and Controls data are included in Volumes 2-18. The Sterility Validation portion for microbiology review is provided in Volume 19. Nonclinical Pharmacology and Toxicology Data are in Volumes 20-42. The Human Pharmacokinetics and Bioavailability Section is contained in Volumes 43-72. The Clinical and Statistical Data Sections are provided in Volumes 73-131 and Volumes 132-161, respectively. Case Report Forms for those subjects who dropped out of the studies due to adverse events are provided in Volume 162 (only in the archival copy of this application).

Together with the paper copy of this NDA, we are also providing 2 CDs of the text and tables of the clinical reports for the dose finding studies (2986 and 2997), the Phase III studies (3010, 3020, 3030), the ISS, ISE, and SAS data sets. These discs are being provided as reviewers' aids together with four additional desk copies of Volume 1.1 (Application Summary Volume). Two additional CDs containing the Application Summary and labeling are also provided.

If you have any questions or require any additional information concerning the information in this NDA, please feel free to contact me or Brian A. Green, Senior Regulatory Affairs Associate, at (978) 851-5981, ext. 220.

Sincerely,

Colin Stewart
President and CEO
ASTA Medica, Inc.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Rainer Skrotzki	Chief Financial Officer
FIRM/ORGANIZATION: ASTA Medica, Inc.	
SIGNATURE: Rainer Skrotzki	DATE: 10/28/99

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

Number of Pages Redacted 4

Confidential,
Commercial Information

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning (please see attached list) (*Name of clinical investigator*), who participated as a clinical investigator in the submitted study (please see attached list) (*Name of clinical study*), is submitted in accordance with 21 CFR part 54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

- any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;
- any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;
- any proprietary interest in the product tested in the covered study held by the clinical investigator;
- any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
Rainer Skrotzki	Chief Financial Officer
FIRM/ORGANIZATION	
ASTA Medica, Inc.	
SIGNATURE	DATE
Rainer Skrotzki	10/28/99

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 4 hours per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FORM FDA 3455 (3/99)

Created by Electronic Document Services/DHHS (301) FT