CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-715

Correspondence

A PROFESSIONAL CORPORATION
205 S. WHITING STREET, SUITE 201
ALEXANDRIA, VIRGINIA 22304

TELEPHONE (703) 751-7777
TELECOPIER (703) 751-2807

November 19, 1996

DC OFFICE
1912 SUNDERLAND PLACE, N.W
WASHINGTON, D.C. 20036-1608
TELEPHONE (202) 296-4444
TELECOPIER (202) 296-7623

ORIG AMENDMENT

Lana L. Pauls, MPH
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
U.S. FOOD AND DRUG ADMINISTRATION
5600 Fishers Lane
Rockville, MD 20657

Re: NDA 20-715
Decapeptyl® Depot 3.75 mg (triptorelin pamoate)
Response to Deficiencies in Microbiology Section

Dear Ms. Pauls:

The information below is provided in response to questions raised in the FDA letter dated October 9. 1996, regarding deficiencies in the Microbiology section of the above-referenced NDA.

Facility and Environmental Control Descriptions

1. ***Please identify the gowning rooms and holding areas on the floor plan of the facilities.***
2. ***Please identify the of each area.***
3. ***Please identify placement of all critical equipment, including .***

Please refer to the revised facility floor plans provided in the pages following, as well as a tabulation listing the and activities conducted in each room of Debio's manufacturing facility. Please note that the production area includes

For ease of review, separate floor plans are provided for critical equipment

A PROFESSIONAL CORPORATION
205 S. WHITING STREET, SUITE 201
ALEXANDRIA, VIRGINIA 22304

TELEPHONE (703) 751-7777
TELECOPIER (703) 751-2807

Orig
BB

October 15, 1996

DC OFFICE
1912 SUNDERLAND PLACE, N.W.
WASHINGTON, D.C. 20036-1608
TELEPHONE (202) 296-4444
TELECOPIER (202) 296-7623

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Drug Evaluation II
5600 Fishers Lane
HFD 580, Room 17B20
Rockville, Maryland 20857

mailed 10/17/96

REC'D
OCT 15 1996
HFD-580

Attn: Lisa Rarick, M.D., Acting Director
Division of Reproductive and Urologic Drug Products

Re: New Drug Application #20-715
Decapeptyl® (triptorelin pamoate for depot suspension) Depot

mailed 10-16

Dear Dr. Rarick,

Reference is made to our letter dated September 6th, 1996 related to the Biopharmaceutics section of the NDA 20-715.

As indicated, we provide you with the remaining two Biopharmaceutics study reports (study R.92.10.98 and Organon 017-001) in an electronic format as described in the table below.

Study code/Summary NDA location	Directory File name	File source File date	 File type
Study R.92.10.98 Vol./Page 1.56/001			
Report by Aster dated 6 May, 1992 (1.56/003-035)		Ipsen-Biotech 4 October, 1996	WordPerfect 5
Report by LASA, part II dated 11 May, 1992, (1.56/175-190)		Ipsen-Biotech 11 September, 1996	WordPerfect 5
Study Organon 017-001 Vol./Page 1.57/001	017-001		
Final report dated 23 November, 1992	017-001	Organon 3 October, 1996	WordPerfect 6.1

We trust that the information supplied adequately addresses the remainder of the questions raised in your letter of August 23, 1996. Should you need further information or have additional questions regarding these matters, please do not hesitate to contact Bob McCormack at Oxford Research International (201-777-2800).

Sincerely,

N. Peter Kostopulos

N. Peter Kostopulos
U.S. Agent

Encl.: 1 diskette
(Study reports: R.92.10.98 and Organon 017-001)

A PROFESSIONAL CORPORATION
205 S. WHITING STREET, SUITE 201
ALEXANDRIA, VIRGINIA 22304

TELEPHONE (703) 751-7777
TELECOPIER (703) 751-2807

DC OFFICE
1912 SUNDERLAND PLACE, N.W.
WASHINGTON, D.C. 20036-1608
TELEPHONE (202) 296-4444
TELECOPIER (202) 296-7623

September 27, 1996

NEW CORRESP

Via Hand Delivery and Telecopier (301) 827-4267

Food and Drug Administration
Center for Drug Evaluation and Research
Documents and Records Section Control (CDR)
12420 Parklawn Drive, Rm 2-14
Rockville, MD 20857

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

Attn: Lisa Rarick, M.D.
Acting Division Director
Division of Reproductive and Urologic Drug Products

Re: New Drug Application #20-715
Decapeptyl® (triptorelin pamoate for depot suspension) Depot

Dear Dr. Rarick:

Enclosed please find, in duplicate, an amendment to NDA No. 20-715 which includes a letter from the Sponsor, Debio R.P., authorizing Bob McCormack of Oxford Research International, Inc. to serve as a contact person for the FDA for technical questions. Also enclosed is a completed form FDA 356h.

I will continue to serve as the Sponsor's U.S. Agent for this NDA, and am authorized to receive all notices and official correspondence from the FDA.

Please feel free to contact me should you have any questions.

Sincerely,

KOSTOPULOS & ASSOCIATES

N. Peter Kostopulos

N. Peter Kostopulos

DEBIO RECHERCHE PHARMACEUTIQUE S.A.

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
5600 Fishers Lane
HFD 580, Room 17B20
Rockville, Maryland 20857

USA

Attn : Lisa Rarick, MD
Acting Director
Division of Reproductive and Urologic Drug Products

Martigny,September 24, 1996/phs

Dear Dr Rarick,

This will serve as an amendment to NDA N° 20-715, Triptorelin Pamoate, which was filed on June 24, 1996.

The purpose of this amendment is to designate Robert McCormack of Oxford Research International ("Oxford") to serve as the contact person for all review questions and technical queries from the FDA reviewers. and assisted the Sponsor, Debio R.P. in assembling the NDA. Debio R.P. is a foreign company, located in Martigny, Switzerland.

N. Peter Kostopulos will continue to serve as the Sponsor's U.S. Agent for this NDA, and is authorized to receive all notices and official correspondence from the FDA.

Best regards,

Dr . P. Orsolini
President

205 S. WHITING STREET, SUITE 201
ALEXANDRIA, VIRGINIA 22304

TELEPHONE (703) 751-7777
TELECOPIER (703) 751-2807

ORIG AMENDMENT

September 6, 1996

DC OFFICE

1912 SUNDERLAND PLACE, N.W.
WASHINGTON, D.C. 20036-1608
TELEPHONE (202) 296-4444
TELECOPIER (202) 296-7623

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation II
5600 Fishers Lane
HFD 580, Room 17B20
Rockville, Maryland 20857

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Attn: Lisa Rarick, M.D.
Acting Director
Division of Reproductive and Urologic Drug Products

Re: New Drug Application #20-715
Decapeptyl® (triptorelin pamoate for depot suspension) Depot

9-26-96

Dear Dr. Rarick:

Reference is made to your letter dated August 23, 1996 in which you requested that additional information be supplied related to the Biopharmaceutics Section of the Decapeptyl® Depot NDA. On behalf of Debio R.P. we are hereby submitting written responses to questions 1 to 4. Additionally, as requested in point number 5, we are enclosing computer diskettes for: the Human Pharmacokinetics and Bioavailability Summary and the following study reports in WordPerfect 6.1 and the raw data related to the reports in an ASCII file format.

Study Code/Summary NDA Location	Directory File Name	File Source File Date	File type
NDA Human Pharmacokinetics and Bioavailability Summary			
Human Pharmacokinetics and Bioavailability Summary Vol./Page 1.1/202-245	Oxford 21 June 1996 Converted from Word 6 5 Sept. 1996		WordPerfect 6.1

Need this

REC'D
SEP 10 1996
HFD-580

This should be received by Brigham in Dallas 10/8/96

Study Code/Summary NDA Location	Directory File Name	File Source File Date	File type
Study DEB-95-TRI-02 Vol./Page 1.52/001	**95TRI02**		
Final report dated 10 June 1996		Inveresk 11 Jun. 1996	WordPerfect 6.1
Appendices to final report (only cover pages & index)		Inveresk 11 Jun. 1996	WordPerfect 6.1
Raw data of testosterone		Inveresk 29 Jul. 1996	ASCII
Raw data of triptorelin		Inveresk 29 Jul. 1996	ASCII
Calculated parameters on testosterone		Inveresk 29 Jul. 1996	ASCII
Calculated parameters on triptorelin		Inveresk 29 Jul. 1996	ASCII
Study DEB-93-TRI-05 Vol./Page 1.55/001	**93TRI05**		
Final report issued September 26th, 1995		Cephac 20 Aug. 1996	WordPerfect 6.1
Raw data of testosterone and triptorelin		Debiopharm 03 Sept. 1996	ASCII Comma delimiter format
Study R.92.10.98 Vol./Page1.56/001	**R921098**		
Raw data of triptorelin and testosterone		Debiopharm 04 Sept. 1996	ASCII Comma delimiter format
Study Organon 017-001 Vol./Page 1.57/001	**017001**		
Raw data of testosterone		Organon 20 Aug. 1996	ASCII Comma delimiter format
Raw data of triptorelin		Organon 20 Aug. 1996	ASCII Comma delimiter format

The text of the remaining two Biopharmaceutics study reports (Study R.92.10.98 and Organon 017-001) from 1992 are currently being obtained from the study trial sponsor in an electronic format. It is anticipated at this point in time that the electronic file for the Organon 017-001 study will be sent to FDA at the end of September, 1996. As of the time of this submission there is no date yet available for obtaining the electronic study report file from the sponsor of the R.92.10.98 trial. We will apprise you of the situation related to this report as soon as information becomes available.

We trust that the information supplied adequately addresses all of the questions raised in your August 23, 1996 letter. Should you have any additional questions or clarifications, please do not hesitate to contact me at (703-751-7777), or Bob McCormack at Oxford Research International (201-777-2800).

Sincerely,

N. Peter Kostopulos

N. Peter Kostopulos, Esq.
U.S. Agent

Encl. Responses to the letter from Dr. L. Rarick dated August 23, 1996 Regarding Additional Biopharmaceutics Information (3 pages)

Table 5.1 Human Pharmacokinetics and Bioavailability Section - Electronic Files of Study Reports, Summary and Raw Data (5 pages)

2 Diskettes: Study reports and raw data
Biopharmaceutics Summary

KOSTOPULOS & ASSOCIATES
A PROFESSIONAL CORPORATION
205 S. WHITING STREET, SUITE 201
ALEXANDRIA, VIRGINIA 22304

TELEPHONE (703) 751-7777
TELECOPIER (703) 751-2807

DC OFFICE
1912 SUNDERLAND PLACE, N.W.
WASHINGTON, D.C. 20036-1608
TELEPHONE (202) 296-4444
TELECOPIER (202) 296-7623

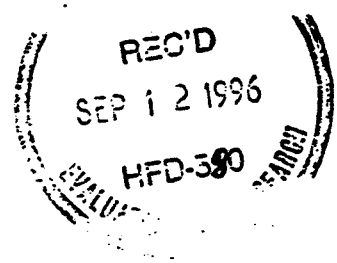
Div'g

NC

September 12, 1996

Via Hand Delivery Telecopier: (301) 827-4267

Ms. Lana Pauls
Consumer Safety Officer
Division of Reproductive and
Urologic Drug Products, HFD-580
Document Control Room 17B-20
FOOD AND DRUG ADMINISTRATION
5600 Fishers Lane
Rockville, MD 20857



rec'd 9-16-96

Re: Debio R.P. NDA #20-715
Triptorelin Pamoate

Dear Ms. Pauls:

I am providing you with the following information from your request of September 10, 1996, concerning the FDA's review of the above-referenced NDA. Please do not hesitate to contact us if you need further information.

Thank you.

rec'd via fax 9/24/96

Sincerely,

KOSTOPULOS & ASSOCIATES

N. Peter Kostopulos

N. Peter Kostopulos

cc: M. Weiner
J. Bueter

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

LAW OFFICES

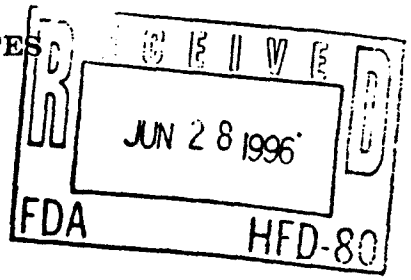
KOSTOPULOS & ASSOCIATES

A PROFESSIONAL CORPORATION

205 S. WHITING STREET, SUITE 201

ALEXANDRIA, VIRGINIA 22304

TELEPHONE (703) 751-7777
TELECOPIER (703) 751-2807



WASHINGTON, D.C. OFFICE

1912 SUNDERLAND PLACE, N.W.
WASHINGTON, D.C. 20036-1608
TELEPHONE (202) 296-4444
TELECOPIER (202) 296-7623

June 24, 1996

Food and Drug Administration
Center for Drug Evaluation and Research
Documents and Records Section Control (CDR)
12420 Parklawn Drive, Rm 2-14
Rockville, Maryland 20857

Attn: Lisa Rarick, M.D.
Acting Division Director
Division of Reproductive and Urologic Drug Products

Re: New Drug Application #20-715
Decapeptyl® (triptorelin pamoate for depot suspension) Depot

Dear Dr. Rarick,

Pursuant to paragraph 505(b) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.50, we are, on behalf of Debio Recherche Pharmaceutique SA (Martigny, Switzerland), submitting, in duplicate, a New Drug Application, NDA #20-715, for Decapeptyl® (triptorelin pamoate for depot suspension) Depot.

Triptorelin pamoate is a synthetic decapeptide agonist analog of naturally occurring lutenizing hormone releasing hormone (LHRH) which acts as a potent inhibitor of gonadotropin secretion when given continuously and in therapeutic doses. As Decapeptyl® Depot, triptorelin pamoate is indicated for the palliative treatment of advanced carcinoma of the prostate. Two triptorelin acetate and two triptorelin pamoate formulations have been approved for marketing in over 60 countries including the United Kingdom (1994), Germany (1986), Switzerland (1986), France (1986) and countries of South America (1989-1995). Decapeptyl® has not been withdrawn from any market for safety or effectiveness reasons, and it is estimated (based on sales) that over [redacted] of use have accrued since its first introductions.

This NDA represents collective experience with triptorelin of over 10 years. The NDA consists of 37 clinical pharmacology studies, 4 controlled and 20 uncontrolled studies and over 30 additional studies in which triptorelin was used for indications other than advanced cancer of the prostate. The core studies, which are principally the three controlled, multicenter clinical trials were identified in the pre-NDA meeting package submission of November 17, 1994 for review by the staff of the Metabolism and Endocrine Drug Products Division. These studies

compared the overall response and survival of 256 patients randomly treated by Decapeptyl® or orchiectomy. This approach (further outlined below) was discussed with, and considered acceptable by, Division staff because of the obvious similarity in structure and activity of Decapeptyl® Depot with the previously approved and marketed LHRH agonists, Lupron Depot and Zoladex. The results from the database for Decapeptyl® Depot support the following conclusions:

- Intramuscular administration of triptorelin at a dose of 3.75 mg (free base) monthly is safe and effective for the palliative treatment of histologically proven stage C or D prostate carcinoma.
- Intramuscular triptorelin is at least as effective as surgical castration in reducing and sustaining plasma testosterone to castrate levels, alleviation of clinical symptoms and two year survival.

Reference is made to the pre-NDA meetings and additional discussions of June 16, 1994, August 11, 1994, January 18, 1995, April 13, 1995, and June 29, 1995, during which representatives of the Metabolism and Endocrine Drug Products Division staff made several recommendations to facilitate the review of the Decapeptyl® Depot NDA. Every effort has been made to address all of the concerns and suggestions of Division staff. We feel that sufficient concurrence has been reached on all of the issues raised by the various reviewers to justify filing of the NDA at this time. The issues raised and how they have been addressed in this application are detailed below.

- *For each of the three European multicenter comparative clinical studies showing the safety and efficacy of triptorelin as an alternative to orchiectomy for the palliative treatment of advanced prostate cancer, provide full analyses, along with CRFs and data tables.*

  Integrated clinical and statistical reports, which present safety and efficacy analyses on both an intent-to-treat and "selected case" basis, are provided for each of three multicenter, controlled, parallel group studies comparing triptorelin and orchiectomy for palliative treatment of prostate cancer. CRFs and data tables also are provided for each study.

- *Were the percentage of patients achieving castration after one month of treatment with triptorelin comparable to those reported for other LHRH agonists?*

  As shown in the integrated clinical and statistical reports for each study, treatment with triptorelin resulted in a reduction of serum testosterone levels similar to those observed in the comparative group of surgically castrated men.

- *How is a meta-analysis justified, given the differences between the three studies in baseline demographics?*

  Integrated safety and efficacy reports are provided instead of a meta-analysis.

- *The equivalence of the acetate formulation used for the clinical studies and the lyophilized pamoate formulation to be marketed in the USA must be demonstrated in a head-to-head comparative study, based on equivalent serum testosterone pharmacodynamics (AUC, t_{max}, t_{cast} and C_{max}) and performed in full compliance with cGCPs. The comparative study also should measure peptide bioavailability (AUC, t_{max}, t_{cast} and C_{max}). Data providing individual/mean serum testosterone and triptorelin levels per formulation per treatment cycle should be provided in separate tables.*

  Equivalent serum testosterone pharmacodynamics of the acetate and lyophilized pamoate formulations were demonstrated in a crossover study in healthy male volunteers. An integrated clinical and statistical report is provided, which includes results of both serum testosterone pharmacodynamic and serum triptorelin pharmacokinetic analyses, assay validation data and data tables which provide individual and mean serum testosterone and triptorelin levels per formulation per treatment cycle in separate tables.

- *In addition to demonstrating the bioequivalence of the two formulations, the NDA also must provide data on the extent of absorption of the triptorelin peptide; the metabolism of the peptide; the protein binding of the peptide; the disposition of triptorelin in patients with compromised liver or renal function; and in vitro data to demonstrate controlled release of the peptide.*

  The bioequivalence section of the NDA provides clinical data demonstrating altered triptorelin clearance in subjects with compromised hepatic or renal function, consistent with published information on metabolism of LHRH agonists; clinical data showing extent of absorption of triptorelin peptide and lack of significant protein binding; and information on the in vitro dissolution test used for product release testing.

- *Major individual impurities as well as stability-indicating impurities must be identified.*

  Data are provided characterizing impurities generated under accelerated conditions and by [redacted] degradation. The major stability-indicating impurity was identified as the [redacted], generated by deamidation of the C-terminal glycylamide group.

We have benefited from the constructive interactions with the Metabolism and Endocrine Drug Products staff and feel that we have adequately responded to all the issues of content and format. Accordingly, we are optimistic and willing to work as closely as necessary with your staff to achieve our mutual goal of having the Decapeptyl® Depot NDA reviewed as rapidly as possible within the current FDA guidelines.

A completed Application to Market a New Drug for Human Use (form FDA 356h) is enclosed. This application consists of 143 volumes which are numbered consecutively, individually paginated and organized in accordance with 21 CFR 314.50. We have provided both a

complete archival copy (blue binders) and a review copy of the volumes. Also, we have provided five additional review copies of the Application Summary so that it can be supplied to each reviewer of the five individual Technical Sections. The binders are color-coded to represent each technical data section. The organization and locations of the various sections of the NDA are listed in Volume 1.1/ page 010 of the Application Summary. In addition, a completed User Fee Cover Sheet (form 3397) is included. User Fee I.D. #3024 has been assigned to the Decapeptyl® Depot NDA, and a check for the amount $102,000, which is 50% of the application fee, has been transmitted electronically to the Food and Drug Administration at the address of Mellon Bank, Pittsburgh, PA.

Be advised that the 120 day Safety Update will be submitted subsequent to this submission.

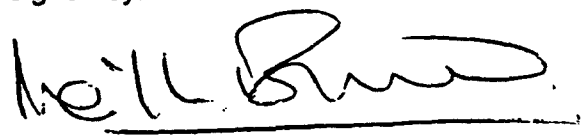
After following the advice of the Metabolism and Endocrine Drug Products Division, we believe this Application to be complete for review by your staff and would look forward to discussing, informally the status of your review in approximately 90 days.

Finally, we would like to draw your attention to the fact that the product, once approved, will be packaged and distributed in the U.S. by Pharmacia & Upjohn, Co. (Kalamazoo, MI), but not under the registered trade name Decapeptyl® Depot.

Should any questions arise during the review of this NDA, we would be pleased to respond. Please contact the undersigned at (703) 751-7777.

Sincerely,

Signed by:



Neil L. Brown, M.Sc., Ph.D.
Executive Director,
Debiopharm S.A., Switzerland
on behalf of and with the approval of
N. Peter Kostopulos
U.S. Agent for
Debio Recherche Pharmaceutique SA

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 20-715

Target Research Associates
Attention: Robert J. McCormick, Ph.D.
Vice President, Regulatory Affairs
554 Central Avenue
New Providence, NJ 07974

JAN 21 200

Dear Dr. McCormick:

We acknowledge receipt on December 16, 1999, of your December 16, 1999, resubmission to your new drug application (NDA) for Trelstar® Depot 3.75 mg (triptorelin pamoate for depot suspension).

This resubmission contains additional Chemistry, Manufacturing and Controls (CMC) information for the to-be-marketed vial alone packaging configuration, responses to CMC deficiencies, relevant CMC, Biopharmaceutic and Microbiology issues, and responses to Clinical deficiencies submitted in response to our June 26, 1997 action letter.

With this amendment, we have received a complete response to our June 26, 1997 action letter.

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

Sincerely,

/S/

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 20-715
HFD-580/Div. Files
HFD-580/JBest
DISTRICT OFFICE

Drafted by: JAB/December, 20, 1999
Initialed by:Rumble,01.20.00
final:JAB/January 20, 2000
filename: N20715ACKltr1299.doc

RESUBMISSION ACKNOWLEDGEMENT (AC)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

OCT 0 1 1999

NDA 20-715

Target Research Associates
Attention: Robert J. McCormack, Ph.D.
1801 East Second Street
Scotch Plains, NJ 07076

Dear Dr. McCormack:

Please refer to your June 26, 1996, new drug application for Decapeptyl (triptorelin) Depot 3.75 mg.

We also refer to your submissions dated May 10, June 18, and September 21, 1999.

You have requested that the packaging configuration for triptorelin be changed from the Debioject single dose delivery system (an enclosed system including diluent, needle, and drug product) to now include vials of triptorelin alone. The following concerns will need to be addressed to support this change:

1. The effects of the use of diluents other than sterile water (such as normal saline, 5% dextrose with half-normal saline, and half-normal saline) on product quality, sterility and bioavailability need to be clarified.

2. The effects of mixing an incorrect quantity of sterile water to the vial on final product quality (including resuspendability) and bioavailability need to be clarified.

3. The effects of using different size syringes and needles on the product quality, sterility, and bioavailability need to be clarified.

4. The Debioject single dose delivery system for triptorelin required injection to the patient within 15 seconds of mixing due to the propensity of the suspension to separate. The supply of triptorelin in vials may lead to delays in injection beyond this timeframe and may affect product quality and bioavailability, and therefore product safety and efficacy.

We have determined that it is appropriate for you to file information regarding the supply of triptorelin in vials as part of your response to the not approvable letter dated June 26, 1997. This response should address the concerns listed above and provide the rationale for marketing the vials alone.

If you have any questions, contact Kim Colangelo, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

/S/ 9/30/99

Lisa Rarick, MD
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Archival NDA 20-715
HFD-580/Div. Files
HFD-580/K.Colangelo
HFD-580/Shames/Rarick/Mann/Rhee/Lin
DISTRICT OFFICE

Drafted by: kmc/September 2, 1999
Initialed by: Rumble, 09.03.99; Lin, 09.07.99; Rhee, 09.08.99; Mann, 09.09.99; Rarick, 09.10.99
Revised: Colangelo, 09.22.99
Initialed by: Moore (for Rumble), 09.22.99; Lin, Rhee, 09.23.99; Shames, Mann, Rarick, 09.24.99
final: Colangelo, 09.27.99
filename: GCCHEM.WPD

GENERAL CORRESPONDENCE

NDA 20-715

JAN 29 1997

Kostopulos & Associates
Attention: Mr. N. Peter Kostopulos
U.S. Agent for Debio R P
205 S. Whiting Street
Suite 201
Alexandria, VA 22304

Dear Mr. Kostopulos:

Please refer to your pending June 24, 1996, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Decapeptyl® (triptorelin pamoate) Depot.

To complete our review of the Medical and Statistical sections of your submission, please respond to the following comments:

Medical

Please submit the following information:

1. The application does not provide information regarding the source of laboratory data for testosterone levels in the three clinical trials. Please provide information on the following:

   a. the location of the laboratories where the testosterone levels from the clinical trials were performed;

   b. the existence of central laboratories for each study; and

   c. laboratory normal testosterone ranges for pre- and post-pubertal men, castrated men, and women, for each of the laboratories utilized in the clinical trials.

2. In the three studies overall, approximately 25% of patients (range: 14.9 - 36.4%) in the orchiectomized group did not have a testosterone level in the castrate range (≤ 1.735 nmol/L) at each monthly determination. Please provide your interpretation of this observation.

3. Loss-to-follow-up (for reasons other than death) appears to be sizable. In the three studies combined, by month 24, only 31% of the Decapeptyl group and 24% of the orchiectomy group remained in the study. Please comment on the implications of these high loss-to-follow-up rates.

4. Two of the study reports state that randomization codes are unavailable and that the studies "cannot strictly speaking be called 'randomized'." Please clarify the randomization procedure for each of the studies. If the studies cannot be considered randomized, please comment on any possible bias that may have been introduced due to non-random treatment allocation.

5. The study reports note that Decapeptyl was administered according to different schedules during the first study month to some or to all patients. For example, in the Palmar study, sustained release Decapeptyl was administered on study days 1, 8 and 28. However, some patients in this study appeared to have received the short acting formulation daily for the first 21 days. In the Botto study, a short acting formulation of Decapeptyl was administered for the first seven days. Please provide the rationale for the use of these regimens (vs. the once monthly regimen). Additionally, please discuss how data using these alternative regimens should be interpreted and how it supports the safety and efficacy of the one-month depot formulation.

6. The study report for the Botto study states that, ". . . the investigator shall control the regularity of the castration level obtained, and if necessary, shorten the time period between injections." Please clarify.

7. In the De Sy study, four patients in the Decapeptyl group had orchiectomy. Please comment on the implications of their change in therapy on the overall results.

8. In the De Sy study, it appears that patients randomized to the orchiectomy group were not informed that they were participating in a clinical trial, nor about the existence of an investigative treatment. Please comment on these circumstances and whether this was the accepted practice in Belgium at the time of the study.

9. We note that after the initial three months, testosterone levels were performed every three-months only. Please comment on the adequacy of this assessment for assuring that Decapeptyl and surgery provided comparable levels of testosterone suppression.

10. In the De Sy study, the total enrollment as stated in the study report (n=60) and in the published manuscript (n=67) differs. Please clarify.

Statistical

Please provide complete documentation (i.e., a code book) for the SAS datasets previously submitted, that explains the variables (demographic, efficacy and safety) for the three individual studies as well as the "pooled" analysis.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact Alvis Dunson, Consumer Safety Officer, at (301) 827-4260.

Sincerely,

/S/

Lisa D. Rarick, M.D.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-715
HFD-580/Div. Files
HFD-580/CSO/ADunson
HFD-580/DShames/HJolson/LKammerman/BTaneja/LPauls
HFD-820/ONDC Division Director (only for CMC related issues)

Drafted by: ADunson/January 27, 1997/n20715ir

Concurrence:
DShames, HJolson, LPauls1.27.97/BTaneja, Lkammerman1.28.97

INFORMATION REQUEST (IR)

NDA 20-715

JAN 10 1997

Debio Recherche Pharmaceutique SA
c/o Kostopulos and Associates
Attention: Mr. N. Peter Kostopulos
205 S. Whiting Street, Suite 201
Alexandria, VA 22304

Dear Mr. Kostopulos:

Please refer to your pending June 24, 1996, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Decapeptyl (triptorelin pamoate) for injection.

We have completed our review of the Environmental Assessment (EA) section of your submission and have identified the following deficiencies:

Section 4c: Description of Proposed Action, Production Locations

If no proprietary intermediates are used in the manufacture of the drug substance, the EA should so state. If proprietary intermediates are used that are manufactured at a facility other than those identified for production of the drug substance and finished product, the EA should identify the location and provide a brief description of the surrounding environment. Any additional production facilities would also have to be addressed under format item 6.

Section 5: Identification of Chemical Substances that are subject to the Proposed Action

The molecular formula should be corrected (H82 rather than H84).

Section 8: Environmental Effects of Released Substances

The information regarding the microbial inhibition studies should be deleted unless the studies are provided so that we can independently evaluate the information in accordance with 40 CFR 1506.5.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact Alvis Dunson, Jr., Consumer Safety Officer, at 301-827-4260.

Sincerely yours,

/S/

Lisa Rarick, M.D.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-715
HFD-580/Div. Files
HFD-580/CSO/ADunson/MRhee
HFD-357/NSager
HFD-820/DNDCII Division Director

Drafted by: ADunson/December 30, 1996/n20715ir

Concurrences:
Lpauls12.30.96/MRhee12.30.96/NSager1.2.97

INFORMATION REQUEST (IR)

NDA 20-715

OCT 9 1996

Debio Recherche Pharmaceutique SA
c/o Kostopulos and Associates
Attention: Mr. N. Peter Kostopulos
205 S. Whiting Street, Suite 201
Alexandria, VA 22304

Dear Mr. Kostopulos:

Please refer to your pending June 24, 1996, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Decapeptyl® (triptorelin pamoate) for injection.

We have completed our review of the Microbiology section of your submission and have identified the following deficiencies:

Facility and Environmental Control Descriptions

1. Please identify the gowning rooms and holding areas on the floor plan of the [redacted] facilities.

2. Please identify the [redacted] of each area.

3. Please identify placement of all critical equipment, [redacted]

Overall Manufacturing Operation

1. Please describe the overall manufacturing operation, [redacted]. The normal flow of the product and components from formulation to finished dosage form should be identified and indicated on the floor plan. Specifications concerning holding periods and critical operations that expose product or product contact surfaces to the environment [redacted] should also be described.

2. How is sterility of the vials and the Debioject delivery system maintained prior to the final assembly?

Sterilization and Depyrogenation of Vials and Debioject Delivery Assembly

1. Information on the percentage of endotoxin recovery from the positive controls should be included.

2. It is not clear if the Debioject delivery assembly (syringe, needle and connector) is [redacted] sterilized prior to filling with sterile WFI. Please specify the sequence of sterilization events for each component.

3. Please provide the cycle parameters and validation data of [redacted] sterilization.

Sterilization of Decapeptyl Vials

1. Please submit the address of the radiation facility.

2. There are contradictions in the information with regard to the material being irradiated for the map load/dose uniformity studies. The protocol on page 42 indicates that empty vials were used for the validation studies. However, the description on page 4 seems to indicate that the validation was performed with vials containing lyophilized powder. Please clarify.

3. Please specify the radiation resistance of the biological indicators.

4. The post-irradiation bacterial counts were given in CFU/g (pages 73 and 74). It is not clear if the spore counts were obtained from the spore strip or from the lyophilized powder. What is the rationale of recovering spores from lyophilized powder if spore strips were used for validation? In addition, please provide a description of the spore recovery after radiation.

Sterilization of the Diluent

1. Please specify the exact sterilization processes for the diluent. In the CMC section, it appears that the diluent was sterilized by [redacted] However, the labeling of the drug product seems to indicate that the diluent was sterilized by [redacted] Please provide the validation protocol, data and specifications of the [redacted]

2. The components that were [redacted] sterilized should be specified. Please provide validation protocol, data and cycle parameters of the [redacted] process.

3. It appears that [redacted] and [redacted] sterilization were employed in the sterilization of the diluent and Debioject delivery system. Please state clearly the sequence of sterilization events of each component from start to finish.

4. Please specify [redacted] residual levels: [redacted], [redacted] levels in the diluent should be mentioned and assessed.

5. What is the penetration ability of [redacted] through the plastic syringe, connector, and needle?

6. How is the sterility maintained for the Debioject delivery system before the final assembly to the [redacted] vial?

Media Fill Studies to Validate the [redacted] Connection of Debioject Delivery System to Decapeptyl Vials

1. Please clarify how the SCD is sterilized. Is sterile SCD filled into the syringes before [redacted] sterilization? Specify the sequence of sterilization events for SCD and syringe components.

2. Please provide the microbiological monitoring data obtained during the media fill runs.

3. Do the procedures for the media fills simulate a normal production fill?

4. Please provide information on the number of units assembled per day, and the number of personnel involved in this operation.

Microbiological Monitoring of the Environment

1. Please clarify the labeling and symbols used in the diagrams on pages 8 to 10. Where are the [redacted]? A key to the numerical representation in these diagrams will be helpful.

2. The number of plates used for each type of monitoring during each filling operation and product assembly should be indicated.

3. We recommend that a periodic monitoring program for yeast, molds, and anaerobic microorganisms be instituted.

Container-closure Integrity

The ability of the container-closure system to maintain the sterility of the drug product throughout its shelf life should be demonstrated. In addition, please submit data validating container-closure integrity of the drug product.

Pyrogen Test for Lot Release

Please supply information on the certification of [redacted] to conduct pyrogen testing.

Stability Programs of the Drug Product

Please provide stability data with regard to container/closure integrity and endotoxin testing at release and at expiry.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact:

Lana L. Pauls, M.P.H.
Chief, Project Management Staff
(301) ~~443-3510~~ 827-4260

Sincerely yours,

/S/ 10-9-96

Lisa Rarick, M.D.
Director
Division of Reproductive and
Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-715
HFD-580/Div. Files
HFD-580/CSO/L.L.Pauls
HFD-580/MJRhee
HFD-805/BUratani
HFD-820/Yuan Yuan Chiu

drafted: LPauls/October 7, 1996/N20715IR.MIC

Concurrences:
BUratani 10.07.96/MRhee 10.08.96

INFORMATION REQUEST (IR)

LLP 10/8/96

NDA 20-715

AUG 23 1996

Debio Recherche Pharmaceutique SA
c/o Kostopulos and Associates
Attention: Mr. N. Peter Kostopulos
205 S. Whiting Street, Suite 201
Alexandria, VA 22304

Dear Mr. Kostopulos:

Please refer to your pending June 24, 1996, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Decapeptyl® (triptorelin pamoate for depot suspension) Depot.

We have completed a preliminary review of the Biopharmaceutic section of your submission and have identified the following deficiencies:

1. Please submit dissolution data/profiles and particle sizes of biolot No. DLGSD-93-08 that was used in bioequivalence (BE) study No. DEB-93-TRI-05.

2. Please provide a summary table of the site(s) of intramuscular (IM) injection employed in the human pharmacokinetics and bioavailability studies and clinical trials.

3. To support the use of hydroalcoholic medium, water:methanol (95:5), and a selected paddle speed of 200 rpm, please provide the following information:

   a. the pH solubility profile of triptorelin;

   b. dissolution data using non-organic solvent(s), including sink condition information at 37°C for various aqueous media; and

   c. the rationale of selecting the above hydroalcoholic solvent as a medium.

4. Because the metabolism of triptorelin was not studied *in vivo*, literature information on the metabolism of triptorelin *in vivo* and/or *in vitro* using Cytochrome P-450 enzymes should be provided, if available.

5. Please submit data in electronic format. Specifically, raw data in ASCII format and Human Pharmacokinetics and Bioavailability summary section as well as individual study reports in WordPerfect (v. 6.1).

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact:

Lana L. Pauls, M.P.H.
Chief, Project Management Staff
~~(301) 443-3510~~ 827-4260
– CORRECTED ON ORIGINAL

Sincerely yours,

/S/ 8/23/96

Lisa Rarick, M.D.
Acting Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-715
HFD-580/Div. Files
HFD-580/CSO/L.L.Pauls
HFD-580/AChen/ADorantes
HFD-820/Yuan Yuan Chiu (with copy of biopharm review)

drafted: LPauls/August 1, 1996/N20715IR.BPH
Concurrences:
AChen, ADorantes 08.06.96, MJRhee, MJRhee for HDavies 08.07.96

INFORMATION REQUEST (IR)

LLP 8/9/96

NDA 20-715

SEP 12 1996

Debio Recherche Pharmaceutique SA
c/o Kostopulos and Associates
Attention: Mr. N. Peter Kostopulos
205 S. Whiting Street, Suite 201
Alexandria, VA 22304

Dear Mr. Kostopulos:

Please refer to your pending June 24, 1996, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Decapeptyl® (triptorelin pamoate for depot suspension) Depot.

Your NDA was deemed acceptable for filing on July 25, 1996.

If you have any questions, please contact me at 301-827-4260.

Sincerely yours,

/S/ 9/11/96

Lana L. Pauls, M.P.H.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-715
HFD-580/Div. Files
HFD-580/CSO/L.L.Pauls

drafted: LPauls/September 11, 1996/N20715AF.LTR

ADVICE

DEBIO RECHERCHE PHARMACEUTIQUE S.A.

Susan Allen, MD
Acting Director,
Division of Reproductive and
Urologic Drug Products
Center for Drug Evaluation and
Research (HFD-580)
Office of Drug Evaluation II
Document Control Room
5600 Fishers Lane
Rockville MD 20857

Martigny, May 17, 2000/PO/phs

Re : NDA 20-715 Trelstar®Depot 3.75 mg
(Triptorelin pamoate for injectable suspension)
Response to request of USAN application

Dear Dr Allen,

Reference is made to the telephone contact with Jeanine Best of May 16, 2000 related to USAN application of Triptorelin pamoate.
Accordingly I hereby declare that Debio R.P. will pursue USAN approval of the name Triptorelin pamoate and will give prompt notification to FDA when USAN approval is granted.

Best regards,

Dr P. Orsolini
President/CEO

DEBIO R.P. s.a., route du Levant 146. C.P. 368. CH-1920 MARTIGNY – Tél. 027/721 79 00 – Fax 027/721 79 01
Groupe DEBIO, rue des Terreaux 17. C.P. CH-1000 LAUSANNE 9 – Tél. 021/311 21 60 – Fax 021/311 21 69

REQUEST FOR A UNITED STATES ADOPTED NAME (USAN)

(For USAN staff use only)

USAN
UNITED STATES ADOPTED NAMES COUNCIL
American Medical Association
P.O. Box 10970
Chicago, Illinois 60610
(312) 464-4416

File No. _____ Acknowledged ____/____/____

INN Status _____ WHO No. _____ Invoice No. _____

SUGGESTED NAME(S) IN ORDER OF PREFERENCE:
(Please submit verification of the absence of conflicts with existing chemical names, insecticides, other nonproprietary names or trademarks)

1. ~~triptorelin pamoate~~
2. _____

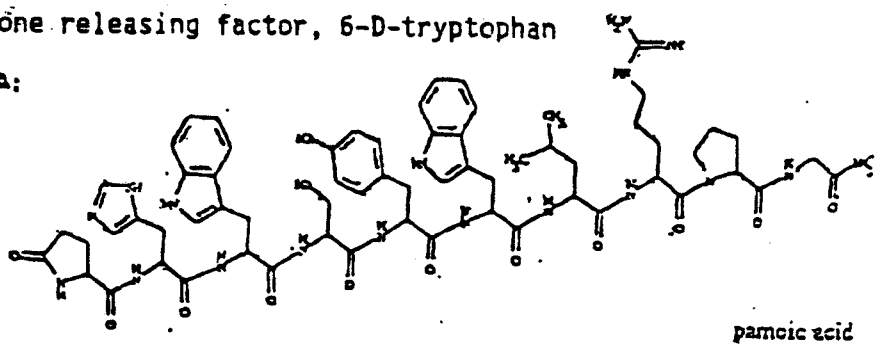
(USAN modified name of salt)

CHEMICAL NAME(S) OR DESCRIPTION:
(Chemical Abstract Service index name must be supplied—see item 2. on back of application form)

(1) 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-tryptophyl-L-leucyl-L-arginyl-L-prolylglycine amide, pamoate salt

(2) Luteinizing hormone releasing factor, 6-D-tryptophan

STRUCTURAL FORMULA:
(Provide stereochemistry)



pamoic acid
$C_{23}H_{16}O_6$

MOLECULAR FORMULA:
$C_{64}H_{84}N_{18}O_{13} \cdot C_{23}H_{16}O_6$

MOLECULAR WEIGHT: 1311.5 + 388.4 = 1699.9

TRIVIAL NAME(S): D-Trp^6- GnRH

CHEMICAL ABSTRACTS SERVICE (CAS) REGISTRY NUMBER:
(Registry number must be supplied—see item 2. on back of application form)
CAS-57773-63-4 for triptorelin (no salt specified)

CODE DESIGNATION(S):

TRADEMARK(S): Decapeptyl^R, Trelstar^R

MANUFACTURER(S): Debio Recherche Pharmaceutique (Martigny, Switzerland)

PRINCIPAL THERAPEUTIC USE(S):* Palliative treatment of advanced prostate cancer

PHARMACOLOGIC ACTION:* GnRH agonist, inhibitor of gonadotropin secretion

*Please provide reference to published literature and copies of key reprints where available. Additional information may be given on an attached sheet. - See attached annotated package insert

1. The process of selecting a USAN should be initiated during that period of investigation when the compound is undergoing clinical studies.

Please indicate the date clinical trials began: 1983 in Europe

IND Application Number(s): IND [redacted] NDA 20-715; submitted under USAN triptorelin

2. The undersigned confirms that the CAS Registry number and Index name are correct. Permission is granted to USAN to utilize this information in USAN-generated publications.

3. Permission is granted for the USAN Council Secretariat to secure the International Union of Pure and Applied Chemistry (IUPAC) chemical name for the compound he with submitted.

4. Permission is granted for the USAN Council Secretariat to submit the negotiated nonproprietary name to the World Health Organization (WHO) Nomenclature Committee for consideration, or if the name is the International Nonproprietary Name (INN), as a matter of information.

5. This submission is made with the understanding that insofar as is known, none of the suggested names are trademarked or the subject of pending registration. It is further understood that the adopted USAN will remain a free and unrestricted nonproprietary name that will not be trademarked.

6. The appropriate user's fee is enclosed. Check one:

- ☐ Name for a single-entity drug (including compounds that have been assigned an International Nonproprietary Name) $5,000.00
- ☒ USAN modified (name for a salt, ester, enantiomer/racemate of a drug for which an adopted USAN already exists) $2,000.00
- ☐ USAN revised (revision of support information used to define a USAN or USAN modified) $750.00
- ☐ Other (explain):

7. Make check payable to American Medical Association/USAN.

SUBMITTED BY:

Applicant: Debio Recherche Pharmaceutique
(name of firm, sponsor or legal representative)

Address: Route du Levant 146
CH-1920 Martigny
Switzerland

Telephone: (011)(41)(27) 721 7900 Telefax: (011)(41)(27) 721 7901

Name of contact person: Piero Orsolini, PhD

Title: President

Signature [signature] Date May 18th 2000

TARGET RESEARCH ASSOCIATES

CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

ORIGINAL

June 15, 2000

Susan Allen, MD
Acting Director, Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation II
Document Control Room
5600 Fishers Lane
Rockville, MD 20857

ORIG AMENDMENT

BL

RE: NDA 20-715
Trelstar™ Depot 3.75 mg
(triptorelin pamoate for injectable suspension)
Submission of final draft labeling-6-15 version

Dear Dr. Allen:

Reference is made to Debio RP NDA 20-715 amendment submitted to FDA on December 16, 1999 and to the June 15, 2000 facsimile message and telephone call from Ms. Jeanine Best in which she requested final changes to the Trelstar™ Depot labeling.

In response, Target Research Associates is hereby submitting in duplicate, on behalf of Debio RP, the final draft Trelstar™ Depot labeling in both electronic and paper copies.

Please contact me if you should have any questions regarding this submission.

Best regards,

Robert J McCormack /gp

Robert J McCormack, Ph.D.
Vice President, Regulatory Affairs

554 Central Avenue • New Providence, NJ 07974 USA • 908/464-7500 • FAX: 908/464-7515

TARGET RESEARCH ASSOCIATES

CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

ORIGINAL

June 13, 2000

Susan Allen, MD
Acting Director, Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation II
Document Control Room
5600 Fishers Lane
Rockville, MD 20857

ORIG AMENDMENT
BL

RE: NDA 20-715
Trelstar™ Depot 3.75 mg
(triptorelin pamoate for injectable suspension)
Submission of final draft labeling

Dear Dr. Allen:

Reference is made to Debio RP NDA 20-715 amendment submitted to FDA on December 16, 1999 and to the June 13, 2000 telephone call from Ms. Jeanine Best in which she requested the final draft labeling.

In response, Target Research Associates is hereby submitting in duplicate, on behalf of Debio RP, the final draft Trelstar™ Depot labeling in both electronic and paper copies.

Please contact me if you should have any questions regarding this submission.

Best regards,

Robert J McCormack/gp

Robert J McCormack, Ph.D.
Vice President, Regulatory Affairs

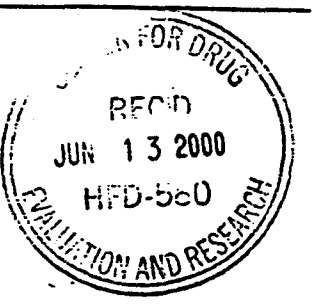
REVIEWS COMPLETED
DOCTOR
CENTER ☐ N.A.I. ☐ MCMO
DATE

554 Central Avenue • New Providence, NJ 07974 USA • 908/464-7500 • FAX: 908/464-7515

TARGET RESEARCH ASSOCIATES

CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

ORIGINAL



June 12, 2000

Susan Allen, MD
Acting Director, Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation II
Document Control Room
5600 Fishers Lane
Rockville, MD 20857

ORIG AMENDMENT

BZ

RE: NDA 20-715
Trelstar™ Depot 3.75 mg
(triptorelin pamoate for injectable suspension)
Response to request by Office Director

Dear Dr. Allen:

Reference is made to Debio RP NDA 20-715 amendment submitted to FDA on December 16, 1999 and to the June 6 and June 9, 2000 telephone calls from Ms. Jeanine Best in which she requested additional information on behalf of the Office Director.

In response, Target Research Associates is hereby submitting in duplicate, on behalf of Debio RP, the following information:

- All AEs (percentage) and the primary efficacy endpoints broken down by Caucasian vs. Black for triptorelin pamoate and leuprolide groups from study DEB-96-TRI-01 first phase.
- Revised Trelstar™ Depot carton and vial label showing the location of the lot number and expiration date.

Please contact me if you should have any questions regarding this submission.

Best regards,

Robert J McCormack, Ph.D.
Vice President, Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

DATE

554 Central Avenue • New Providence, NJ 07974 USA • 908/464-7500 • FAX: 908/464-7515

TARGET RESEARCH ASSOCIATES

CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

ORIGINAL

June 8, 2000

Susan Allen, MD
Acting Director, Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation II
Document Control Room
5600 Fishers Lane
Rockville, MD 20857

ORIG AMENDMENT

DL

RE: NDA 20-715
Trelstar™ Depot 3.75 mg
(triptorelin pamoate for injectable suspension)
Revised package insert

Dear Dr. Allen:

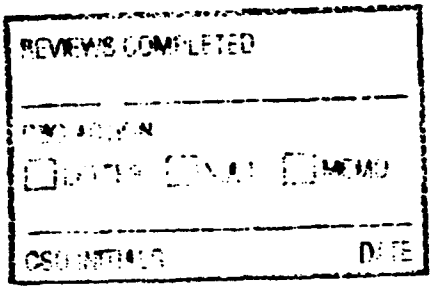
Reference is made to Debio RP NDA 20-715 amendment submitted to FDA on December 16, 1999 and to the June 6, 2000 fax of Ms. Jeanine Best, which requested further revisions to the Trelstar™ package insert.

In response, Target Research Associates is hereby submitting in duplicate, on behalf of Debio RP, the package insert with all revisions requested by the agency up to June 6, 2000. Please be advised that a correction of the % Caucasian data has been made. Please contact me if you should have any questions regarding this submission.

Best regards,

Robert J McCormack Ph.D.

Robert J McCormack, Ph.D.
Vice President, Regulatory Affairs



554 Central Avenue • New Providence, NJ 07974 USA • 908/464-7500 • FAX: 908/464-7515

TARGET
RESEARCH
ASSOCIATES

CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

ORIGINAL

June 5, 2000

Susan Allen, MD
Acting Director, Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation II
Document Control Room
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-715
Trelstar™ Depot 3.75 mg
(triptorelin pamoate for injectable suspension)
Revised package insert

ORIG AMENDMENT

BL

Dear Dr. Allen:

Reference is made to Debio RP NDA 20-715 amendment submitted to FDA on December 16, 1999 and to the May 31, 2000 fax of Ms. Jeanine Best, which requested further revisions to the Trelstar™ package insert.

In response, Target Research Associates is hereby submitting in duplicate, on behalf of Debio RP, the following information:

Package insert with all revisions requested by the agency up to May 31, 2000. Please contact me if you should have any questions regarding this submission.

Best regards,

Robert J McCormack

Robert J McCormack, Ph.D.
Vice President, Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

DATE

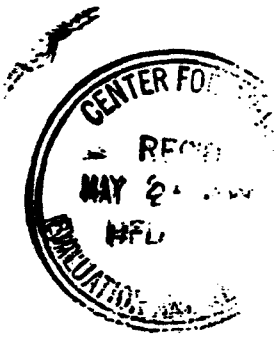
CSO INITIALS

554 Central Avenue • New Providence, NJ 07974 USA • 908/464-7500 • FAX: 908/464-7515

TARGET RESEARCH ASSOCIATES

CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

ORIGINAL



May 23, 2000

Susan Allen, MD
Acting Director, Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation II
Document Control Room
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-715
Trelstar™ Depot 3.75 mg
(triptorelin pamoate for injectable suspension)
Safety Update Information

AMENDMENT

S4

Dear Dr. Allen:

Reference is made to Debio RP NDA 20-715 amendment submitted to FDA on December 16, 1999 and to the May 18, 2000 request of Ms. Jeanine Best for a statement regarding submission of additional safety information to NDA 20-715.

In response, Target Research Associates is hereby submitting in duplicate, on behalf of Debio RP, a confirmation by Debio that all clinical studies were complete at the time of filing of the NDA 20-715 amendment, therefore there is no additional safety information to report.

Please contact me if you should have any questions regarding this submission.

Best regards,

Robert J McCormack, Ph.D.
Vice President, Regulatory Affairs

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

554 Central Avenue • New Providence, NJ 07974 USA • 908/464-7500 • FAX: 908/464-7515

DEBIO PHARM S.A.

Susan Allen, MD
Acting Director,
Division of Reproductive and
Urologic Drug Products
Center for Drug Evaluation and Research
(HFD-580)
Office of Drug Evaluation II
Document Control Room
5600 Fishers Lane
Rockville MD 20857

Lausanne, May 19, 2000

Dear Dr Allen,

I hereby confirm that all clinical studies submitted in NDA 20-715 were complete at time of amendment submission (December 16, 1999), therefore there is no additional safety information to report.

Sincerely,

Hervé Porchet, M.D.
Director, Clinical Pharmacology

DEBIOPHARM S.A. DÉVELOPPEMENTS BIOLOGIQUES ET PHARMACEUTIQUES / LAUSANNE

Rue des Terreaux 17 – Case postale 211 – CH-1000 Lausanne 9 (Switzerland) – Tél. +41 21/321 01 11 – Fax +41 21/321 01 69

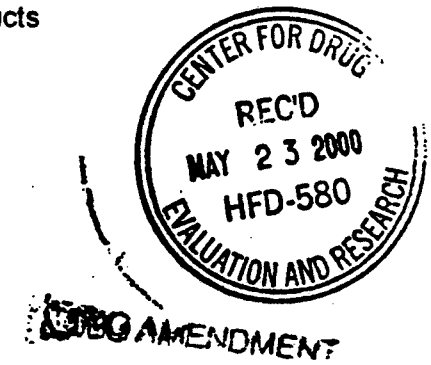
TARGET
RESEARCH
ASSOCIATES

CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

ORIGINAL

May 22, 2000

Susan Allen, MD
Acting Director, Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation II
Document Control Room
5600 Fishers Lane
Rockville, MD 20857



BL

RE: NDA 20-715
Trelstar™ Depot 3.75 mg
(triptorelin pamoate for injectable suspension)
Revised package insert

Dear Dr. Allen:

Reference is made to Debio RP NDA 20-715 amendment submitted to FDA on December 16, 1999 and to the May 22, 2000 fax of Ms. Jeanine Best which requested further revisions to the Trelstar™ package insert.

In response, Target Research Associates is hereby submitting in duplicate, on behalf of Debio RP, the following information:

Package insert with all revisions requested by the agency up to May 22, 2000 (AM). The package insert is being provided as both paper and electronic copies. Please contact me if you should have any questions regarding this submission.

Best regards,

Robert J McCormack, Ph.D.
Vice President, Regulatory Affairs

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ORIGINAL

TARGET RESEARCH ASSOCIATES

CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

BL

ORIG AMENDMENT

May 19, 2000

Susan Allen, MD
Acting Director, Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation II
Document Control Room
5600 Fishers Lane
Rockville, MD 20857

RE: **NDA 20-715**
Trelstar™ Depot 3.75 mg
(triptorelin pamoate for injectable suspension)
Response to FDA request

Dear Dr. Allen:

Reference is made to Debio RP NDA 20-715 amendment submitted to FDA on December 16, 1999 and to communications with Jeanine Best on May 15, 16, and 19, 2000 during which revisions to the package insert, and Trelstar™ cartons were requested by the agency. In addition, a request was made by Ms. Best for USAN information.

In response, Target Research Associates is hereby submitting in duplicate, on behalf of Debio RP, the following information:

- Package insert with all revisions requested by the agency up to May 19, 2000 (AM). The package insert is being provided as both paper and electronic copies. Please be advised that [redacted] has been changed to Trelstar™.
- Revised carton and vial mock ups
- USAN application
- USAN commitment letter

Please contact me if you should have any questions regarding this submission.

Best regards,

Robert J McCormack, Ph.D.
Vice President, Regulatory Affairs

REVIEWS COMPLETED
CSO ACTI
☐ LETTE ☐ MEMO
CSO INIT: DATE

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TARGET
RESEARCH
ASSOCIATES

CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

ORIGINAL

May 15, 2000

Susan Allen, MD
Acting Director, Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation II
Document Control Room
5600 Fishers Lane
Rockville, MD 20857

ORIG AMENDMENT
BL

RE: NDA 20-715
Trelstar® Depot 3.75 mg
(triptorelin pamoate for injectable suspension)
Response to FDA request for Trelstar cartons and labels

Dear Dr. Allen:

Reference is made to Debio RP NDA 20-715 amendment submitted to FDA on December 16, 1999 and to a telephone contact by Jeanine Best on May 1, 2000. During the call Ms. Best stated that Dr. Lin needs mock ups of all Trelstar cartons and labels.

In response, Target Research Associates is hereby submitting in duplicate, on behalf of Debio RP, copies of the individual vial carton and individual vial label for Trelstar®.

Please contact me if you should have any questions regarding this submission.

Best regards,

Robert J McCormack, Ph.D.
Vice President, Regulatory Affairs

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DEBIO RECHERCHE PHARMACEUTIQUE S.A.

ORIGINAL

BC
ORIG AMENDMENT

Susan Allen, MD
Acting Director,
Division of Reproductive and
Urologic Drug Products
Center for Drug Evaluation and
Research (HFD-580)
Office of Drug Evaluation II
Document Control Room
5600 Fishers Lane
Rockville MD 20857

Martigny, May 11, 2000/PO/ep

Re : NDA 20-715 Trelstar®Depot 3.75 mg
(Triptorelin pamoate for injectable suspension)
Response to request from chemistry reviewer

Dear Dr Allen,

Reference is made to the telephon contact with Jeanine Best of May 9, 2000 related to Dr Lin's request. Accordingly I hereby declare that Debio R.P. will manufacture the to be marketed Trelstar®Depot 3.75 mg with the [redacted] only.

Best regards,

Dr P. Orsolini
President/CEO

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ [illegible]

CSO INITIALS DATE

DEBIO R.P. s.a., route du Levant 146, C.P. 368, CH-1920 MARTIGNY – Tél. 027/721 79 00 – Fax 027/721 79 01
Groupe DEBIO, rue des Terreaux 17, C.P., CH-1000 LAUSANNE 9 – Tél. 021/311 21 60 – Fax 021/311 21 69

TARGET
RESEARCH
ASSOCIATES

CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

ORIGINAL

May 11, 2000

Susan Allen, MD
Acting Director, Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation II
Document Control Room
5600 Fishers Lane
Rockville, MD 20857

BC
ORIG AMENDMENT

RE: **NDA 20-715**
Trelstar® Depot 3.75 mg
(triptorelin pamoate for injectable suspension)
Response to revised dissolution specifications

Dear Dr. Allen:

Reference is made to Debio RP NDA 20-715 amendment submitted to FDA on December 16, 1999 and to the May 10, 2000 teleconference between Ms. Jeanine Best, Trelstar® Regulatory Project Manager, Dr. David Lin, Chemistry Reviewer and Target Research Associates, US Agent for Debio RP. During the teleconference Dr. Lin stated that the Division would like to propose dissolution specifications for the to be marketed Trelstar® which are different than those set by Debio RP. The dissolution specifications proposed by FDA are as follows:

- 1 hour [redacted]%*
- [redacted] hours [redacted]%*
- [redacted] hours [redacted]%*

* = mean % ± absolute 10 %

On behalf of Debio RP, we are submitting in duplicate, notification to the agency that Debio RP accepts the dissolution specifications proposed by FDA for Trelstar®.

Please contact me if you should have any questions regarding this submission.

Best regards,

Robert J McCormack, Ph.D.
Vice President, Regulatory Affairs

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

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TARGET RESEARCH ASSOCIATES

CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

ORIGINAL

May 9, 2000

Susan Allen, MD
Acting Director, Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation II
Document Control Room
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-715
Trelstar® Depot 3.75 mg
(triptorelin pamoate for injectable suspension)
Submission of revised draft labeling

ORIG AMENDMENT
BL

Dear Dr. Allen:

Reference is made to Debio RP NDA 20-715 amendment submitted to FDA on December 16, 1999 and to the May 1 facsimile which contained initial label revisions requested by FDA and label comments made by FDA.

On behalf of Debio RP, we are submitting in duplicate, the edited label which, incorporates FDA's requested changes and also changes suggested by Debio RP and Pharmacia & Upjohn. Please be advised that the edited label is being provided as both a paper and electronic copy in Word 97 format.

Please contact me if you should have any questions regarding this submission.

Best regards,

Robert J McCormack, Ph.D.
Vice President, Regulatory Affairs

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

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TARGET RESEARCH ASSOCIATES

CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

May 5, 2000

Jeanine A. Best, MSN, RN
Regulatory Project Manager
Division of Reproductive and Urologic Drug Products (HFD-580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
Parklawn Building, Room 17B-45
5600 Fishers Lane
Rockville, MD 20857

ORIG AMENDMENT
BC

Re: NDA 20-715
Trelstar®Depot 3.75 mg (triptorelin pamoate for injectable suspension)
Response to FDA Question on *In Vitro* Dissolution Test Specifications

Dear Ms. Best:

At the teleconference on April 20, 2000, FDA chemistry reviewers requested comparative *in-vitro* dissolution data for the Trelstar biobatches manufactured using the [redacted] determine the concentration of the reference standard and the [redacted] method in which the concentration of the reference standard is determined by dilutions in the [redacted]

The first comparison of the two [redacted] methods for dissolution testing was performed for batch #D601D01K7, at which time the switch to the [redacted] dilution method was made. In the past week, additional comparative testing was performed for two recent process validation batches. Results of comparative testing, summarized in Table 1 on the pages following, showed that results obtained using the [redacted] method were an average of [redacted]% lower than those obtained using the [redacted] method.

Although data presented previously in the NDA listed only three biobatches manufactured using the [redacted] which had been used in studies that generated AUC data (see Table 3, NDA amendment 20-715, volume 2.1, page 122), a review of clinical data showed that five different batches had been used in studies DEB-96-TRI-01 and DEB-98-TRI-01; results of these studies are presented by batch in Table 2 on the pages following. In order to establish dissolution test specifications based on these five biobatches, the *in vitro* dissolution release test results for those batches that had been obtained using the [redacted] method were adjusted [redacted]% lower, based on the results of comparative

testing. As shown in Table 3 on the pages following, the mean ± 10% for these five biobatches, obtained using the calculated values for the [redacted] method, did not encompass the release test values obtained at each individual test point for biobatch D601D01K7 and at the [redacted] hr test point for biobatch D60102027. Accordingly, we propose to establish *in vitro* dissolution release test specifications based on ±10% of the low and high values obtained for release testing of the biobatches at each test point. As shown in Table 3, these *in vitro* dissolution release test specifications are [redacted] percent peptide dissolved at [redacted] hr, [redacted] percent peptide dissolved at [redacted] hr, and [redacted] percent peptide dissolved at [redacted] hr. These specifications are much narrower than those proposed previously.

We propose to set stability test specifications at [redacted]% of the low and high values obtained for the release testing of the biobatches at each test point. Accordingly, based on data in Table 3, the stability specifications for the *in vitro* dissolution test will be set at

[redacted] percent peptide dissolved at [redacted] hr, [redacted] percent peptide dissolved at [redacted] hr, and [redacted] percent peptide dissolved at [redacted] hr.

Should you have any questions, please do not hesitate to contact me at 908-464-7500.

Sincerely,

Robert J. McCormack, Ph.D.
Vice President, Regulatory Affairs
Target Research Associates

REVIEWS COMPLETED

CSO ACTION:

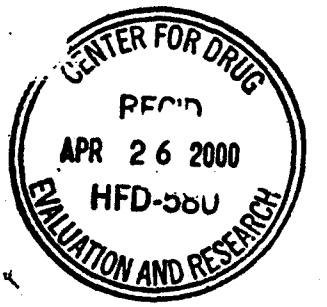
☐ LETTER ☐ N.A.I. ☐ MEMO

INITIALS DATE

TARGET RESEARCH ASSOCIATES

CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

ORIGINAL



April 25, 2000

Susan Allen, MD
Acting Director, Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation II
Document Control Room
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-715
Trelstar® Depot 3.75 mg
(triptorelin pamoate for injectable suspension)
Response to request for additional information

ORIG AMENDMENT

BM

Dear Dr. Allen:

Reference is made to Debio R.P. NDA 20-715 amendment submitted to FDA on December 16, 1999 and to a telephone contact from Jeanine Best on April 12, 2000 during which time she requested, on behalf of the medical reviewer, that a spreadsheet with the following column headings be submitted for study DEB-96-TRI-01 (second phase), in both electronic and paper format:

- Patient I.D. #
- Treatment Arm
- Baseline testosterone levels
- Month 1 – Castration levels achieved? (Yes, No, or Missing)
- Month 1 – Testosterone level
- Month 2 – Castration levels achieved? (Yes, No, or Missing)
- Month 2 – Testosterone level
- Month 3 – Was castration level maintained? (Yes, No, or Missing)
- Month 3 – Testosterone level
- Month 3 – LH at Time 0
- Month 3 – LH at 2 hours
- Month 3 – Testosterone at 2 hours (Subset of 15 patients)
- Month 4,5,6,7,8,9 – Was castration level maintained? (Yes, No, or Missing)
- Month 4,5,6,7,8,9 – Testosterone level

Therefore, as requested, Target Research Associates is hereby submitting in duplicate, on behalf of Debio R.P., an Excel spreadsheet with the above mentioned column headings for patients who participated in study DEB-96-TRI-01 (second phase). This information can also be located on the accompanying diskette).

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Please contact me if you should have any questions regarding this submission.

Best regards,

Robert J. McCormack, Ph.D.
Vice President, Regulatory Affairs

TARGET
RESEARCH
ASSOCIATES

CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

April 24, 2000

Susan Allen, MD
Acting Director, Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation II
Document Control Room
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-715
Trelstar® Depot 3.75 mg
(triptorelin pamoate for injectable suspension)
Response to request for additional information

Dear Dr. Allen:

Reference is made to Debio R.P. NDA 20-715 amendment submitted to FDA on December 16. 1999 and to the April 18 2000 telephone contact of Jeanine Best in which additional information was requested on behalf of the medical reviewer. We are submitting in duplicate. on behalf of Debio R.P., the following information requested by the medical reviewer:

- For study 96-TRI-01 first phase: each testosterone level through 9 months for the patients who did not achieve castration levels at day 29. Please be advised that there are only 12 patients who did not achieve castration at Day 29 not 13 as stated in the April 18 telephone request.

- Individual serum testosterone levels through 9 months for patients who did not maintain castration

The above information is being provided electronically in excel format and as a paper copy. Please let me know if you have any questions or need additional information.

Best regards.

Robert J McCormack, Ph.D.
Vice President. Regulatory Affairs

554 Central Avenue • New Providence, NJ 07974 USA • 908/464-7500 • FAX: 908/464-7515

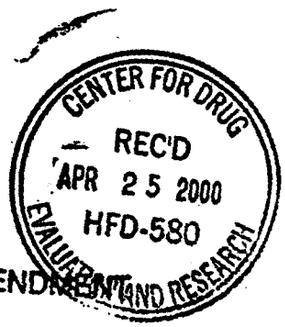
TARGET RESEARCH

CLINICAL RESEARCH, REGULATORY AFFAIRS & BIOSTATISTICS

April 24, 2000

ORIGINAL

Susan Allen, MD
Acting Director, Division of Reproductive and Urologic Drug Products
Center for Drug Evaluation and Research (HFD-580)
Office of Drug Evaluation II
Document Control Room
5600 Fishers Lane
Rockville, MD 20857



RE: NDA 20-715
Trelstar® Depot 3.75 mg
(triptorelin pamoate for injectable suspension)
response to request for additional information

ORIG AMENDMENT

BB

Dear Dr. Allen:

Reference is made to Debio R.P. NDA 20-715 amendment submitted to FDA on December 16, 1999 and to the following telephone contacts from Jeanine Best:

- On April 13, 2000 Ms. Best called and requested, on behalf of the biopharmaceutics reviewer, that the testosterone concentration data for both individual data as well as mean values be provided as Excel spreadsheets for studies 96-TRI-01 (first and second phase) and 98-TRI-01, in both electronic and paper format.
- On April 18, 2000 Ms. Best called and requested that electronic copies of the study synopsis for studies 98-TRI-01, 96-TRI-01, and 96-TRI-02 be provided in Word format.

Therefore, on behalf of Debio RP, the following information is being submitted in duplicate:

- Testosterone concentrations for both individual data and mean values for studies 96-TRI-01 (first and second phase) and 98-TRI-01, in both paper and electronic format. The table below identifies the study and the name of the Excel file where the information can be located on the accompanying diskette.

Study	Excel File Name
96-TRI-01 first phase	
96-TRI-01 second phase	
98-TRI-01	

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- Individual study synopsis for studies 96-TRI-01, 96-TRI-02, and 98-TRI-01, in electronic study synopsis can be located on the accompanying diskette.

Study	Word File Name
96-TRI-01 1st Phase	
96-TRI-01 2nd Phase	
96-TRI-02	
98-TRI-01	

Please contact me if you should have any questions regarding this submission.

Best regards,

Robert J. McCormack, Ph.D.
Vice President, Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION

☐ LETTER ☐ MEMO

CSO INIT: DATE