CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-715

Administrative Documents

Item 13

Patent Information Statement

In accordance with 21 C.F.R. §314.53, Debio R.P. represents that the NDA is based upon three drug product patents, described as follows:

US Patent No. 5,134,122. Expiration date: July 20, 2010. Drug product patent. Patent holder: Debio R.P. Case postale 368, Route du Levant 146, CH-1920 Martigny, Switzerland.

US Patent NO. 5,225,205. Expiration date: July 20, 2010. Drug product patent. Patent holder: Debio R.P. Case postale 368, Route du Levant 146, CH-1920 Martigny, Switzerland.

US Patent NO. 5,192,741. Expiration date: March 9, 2010. Drug product patent. Patent holder: Debio R.P. Case postale 368, Route du Levant 146, CH-1920 Martigny, Switzerland.

The US agent of the patent holder and applicant, authorized to receive notice of patent certification under §505 (b) (3) and (j) (2) (B) of Title 21 and §§314.52 and 314.95 of 21 C.F.R. is N. Peter Kostopulos, Kostopulos & Associates, 205 S. Whiting Street, Suite 201, Alexandria, Virginia 22304.

Formulation Patent Declaration: With respect to each of the aforementioned patents, applicant submits the following:

The undersigned declares that Patent Nos. 5,134,122, 5,225,205, and 5,192,741 cover the formulation and composition of Triptorelin Pamoate. This product is the subject of this application for which approval is being sought.

Piero Orsolini, President
Debio R.P.

NDA 20715
Decapeptyl™ (triptorelin pamoate)

June 26, 1997

Exclusivity Summary

Not required at this time because the application will be not approved.

EXCLUSIVITY SUMMARY FOR **NDA # 20-715**

Trade Name: **Trelstar®** Generic Name: **triptorelin pamoate for injectable suspension**

Applicant Name: **Debio Recherche Pharmaceutique S.A. HFD # 580**

Approval Date If Known: **June 15, 2000** during this review cycle

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /X/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /X/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /X/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /_ __/ NO /_ X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

_____No_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /__/ NO /X/

If yes, NDA #

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES / / NO /_X_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /_ _/ NO / /

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES / / NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES / / NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO / /

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO / /

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO / /

If yes, explain

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO / /

Investigation #2 YES /___/ NO / /

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO / /

Investigation #2 YES /___/ NO / /

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

YES / / ! NO /___/ Explain: _____
!

Investigation #2 !
!
YES / / !-NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
!
YES /___/ Explain _____ ! NO /___/ Explain _____
!
_____ ! _____
!
_____ ! _____
!
!

Investigation #2 !
!
YES /___/ Explain _____ ! NO /___/ Explain _____
!
_____ ! _____
!
_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /__/ NO / /

If yes, explain: _____

_____

/S/ 5/18/00

Signature Date

Title: Regulatory Project Manager

/S/ 5/29/00

Signature of Office/ Date
Division Director

cc: Original NDA Division File HFD-93 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20715	**Trade Name:**	DECAPEPTYL (TRIPTORELIN) DEPOT 3.75MG
Supplement Number:		**Generic Name:**	TRIPTORELIN
Supplement Type:		**Dosage Form:**	INJ
Regulatory Action:	AP	**Proposed Indication:**	Palliative treatment of advanced prostate cancer

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No waiver and no pediatric data

What are the INTENDED Pediatric Age Groups for this submission?

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

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

Label Adequacy	Does Not Apply
Formulation Status	-
Studies Needed	-
Study Status	-

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

COMMENTS:

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

/S/ MSN NN 6/15/00

Signature Date

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-715 Trade (generic) names DECAPEPTYL (triptorelin pamoate)

Check any of the following that apply and explain, as necessary, on the next page:

____ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

____ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

____ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

____ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)

____ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

____ a. The applicant has committed to doing such studies as will be required.

____ (1) Studies are ongoing.
____ (2) Protocols have been submitted and approved.
____ (3) Protocols have been submitted and are under review.
____ (4) If no protocol has been submitted, on the next page explain the status of discussions.

____ b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

✓ 4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

____ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items: _____

/S/

Signature of Preparer

4/23/97

Date

cc: Orig NDA
HFD-___/Div File
NDA Action Package

DEBIO RECHERCHE PHARMACEUTIQUE S.A.

I, Piero Orsolini, of Debio Recherche Pharmaceutique S.A. in my capacity as President & CEO, certify in accordance with the requirements of the Generic Drug Enforcement Act of 1992 (Pub. L. No. 102-282, 306 (k), 106 Stat. 149, 158) that Debio Recherche Pharmaceutique S.A., in connection with this NDA has not and will not use in any capacity the services of any person (including a corporation, partnership, association or individual) who has been debarred from submitting or assisting in the submission of a drug application to the Food and Drug Administration by the Secretary of Health and Human Services pursuant to Authority conferred to the Secretary under section 306 (a), and section 306 (b), 106 Stat. 149, 150-152 (1992)).

Date : 2- May 1996

Signature : 

Administration CH-1000 Lausanne 9, rue des Terreaux 15-17, case postale 82, telephone +41/21 311 21 60 fax +41/21 311 21 65
Laboratoire CH-1920 Martigny, route du Levant 146, case postale 348 telephone +41/26 22 33 83 fax +41/26 22 33 65

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JUN 15 200

MEMORANDUM

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

DATE: June 13, 2000

FROM: Florence Houn MD MPh

SUBJECT: Office Director Memo

TO: NDA 20-715 Trelstar™ (triptorelin pamoate for suspension injection)

This memo supports to the Division of Reproductive and Urologic Drug Product's recommendation to approve Debio Recherche Pharmaceutique's application to market triptorelin pamoate, a new molecular entity with the established name Trelstar ™. The company proposes Trelstar ™ be indicated in the palliative treatment of advanced prostate cancer. The reviews of the Division state the analysis of the new active control trial data should proceed without the post-hoc pooling of other smaller trials. The primary efficacy endpoint was both achievement of castration at one month and maintenance of castration through nine months. I concur with the Division's assessment that although non-inferiority for the first half of the efficacy endpoint was not met by day 29, a closer look at the non-responders (n=12) showed response of 11 of the 12 within day 57 and there was maintenance of response. These results are clinically meaningful.

Looking across studies to assess validity of control arm response is problematic because different studies are conducted in different populations under different medical conditions. The sponsor proposed that non-inferiority should have been met because the current trial's active control response was exceptionally high compared to the active control's response rates in trials leading to its approval (91%, 92%, 94% and 97% in historical trials versus 99% in the current trial). However, 99% would be included in the 95% confidence interval range for many of these trials. This proposed line of reasoning was not accepted.

There is no safety signal in the safety database. The Office of Post-marketing Drug Risk Assessment has been alerted that gonadotropin agonists may cause hypersensitivity reactions.

Because this trial has enrolled substantial numbers of blacks from South Africa, it offers a rare opportunity to look at efficacy and safety by race. On June 5, 2000 the FDA requested analyses of the primary efficacy variable and a frequency distribution of adverse events stratified by race. This was received on June 9, 2000. The data showed no difference in how Caucasians and Blacks/Coloreds (terminology in the database) responded to Trelstar and in the distribution of adverse events. There may be a suggestion of racial differences with respect to how the active control maintains castration response, but this would need further exploration and studies. This issue will be discussed further in the division.

The Division and the company have agreed to labeling.

MAY 30 2000

Division Director Memorandum

NDA#:	20-715
Sponsor:	Debio Recherche Pharmaceutique, S.A.
Drug:	Trelstar™ Depot 3.75 mg (triptorelin pamoate)
Indication:	Palliative treatment of advanced prostate cancer
Dosage and administration:	3.75 mg intramuscularly once every month
Date of submission:	December 16, 1999
Date of memorandum:	May 29, 2000

Background:

Triptorelin is an agonist analog of gonadotropin releasing hormone (GnRH) that has been marketed in several countries as an acetate or pamoate salt for the treatment of advanced prostate cancer. An original new drug application (NDA) for this product was submitted to the FDA on June 26, 1996. The application contained the results from three studies conducted in the 1980s in which triptorelin pamoate was administered monthly by intramuscular (IM) injection for palliation of advanced prostate cancer. The application was found to be seriously deficient by multiple review disciplines. As a result, the sponsor received a not-approvable letter from the Division of Reproductive and Urologic Drug Products (DRUDP) on June 26, 1997. The current submission consists of a complete response to the not-approvable letter of 1997.

Current Submission:

This submission contains results from a study (e.g., study DEB-96-TRI-01) consisting of two phases. The "first phase" of this trial was ongoing at the time of the not-approvable action in June of 1997. This phase of the study consisted of a comparative trial of a 1-month and a 3-month IM formulation of triptorelin pamoate.

At the suggestion of DRUDP, the sponsor conducted a second phase of this study comparing the 1-month formulation of triptorelin pamoate to a 1-month formulation of Lupron® Depot. The goal of the "second phase" of this study was to demonstrate "non-inferiority" of triptorelin 1-month depot to Lupron 1-month depot based upon achievement of castrate levels of testosterone at one month and maintenance of those levels from months two to nine of treatment. Non-inferiority would be demonstrated by showing that the castration incidence and maintenance percentages in the triptorelin-treated group were no more than 10% less than those in the Lupron® Depot-treated group. As described in the primary and secondary clinical reviews, 91.2% of 137 patients receiving triptorelin pamoate in this phase of the study achieved castrate levels of serum testosterone on day 29 as compared to 99.3% of Lupron-treated patients. The lower bound of a one-sided 95% confidence interval for the point estimate of the difference in achievement of

castration rates between the treatment arms was –15.7%, thereby failing to meet the predetermined statistical test for non-inferiority with Lupron® Depot.

The sponsor attempted to explain these results by noting that the "achieve castration rate" for the Lupron® Depot-treated arm of this study (e.g., 99.3%) was much higher than rates seen in previous phase 3 trials upon which U.S. marketing approval of Lupron® Depot had been based (e.g., 91%, 92%, 94% and 97%). As described in the primary and secondary clinical reviews, three other studies or analyses did provide evidence of the efficacy of triptorelin pamoate in achieving castration with regard to historical controls: 92.7% of 164 patients in the first phase of trial DEB-96-TRI-01 achieved castration by day 29; 93% of 32 patients in trial DEB-96-TRI-02 achieved castration by day 29; 100% of 13 patients in trial DEB-98-TRI-01 achieved castration on day 29.

Maintenance of castrate testosterone levels by triptorelin pamoate for months two to nine of treatment was demonstrated in both phases of trial DEB-96-TRI-01. As noted in the clinical reviews, this endpoint may have greater clinical significance than achievement of castrate testosterone levels *by month one of treatment* in patients with advanced prostate cancer, many of whom will require long-term drug administration for sustained testosterone suppression. In addition, the rate of acute-on-chronic LH release and subsequent testosterone flare at months three and six of dosing was noted to be comparable between the triptorelin pamoate- and the Lupron® Depot-arms of both phases of study DEB-96-TRI-01.

Data contained in the current submission supported the safety of triptorelin pamoate for the palliative treatment of advanced prostate cancer. Although hypersensitivity reactions are associated with use of GnRH agonists, there was no evidence of clinically significant hypersensitivity reactions from the study results contained in the current submission.

Other discipline review issues:

Two chemistry issues of importance arose during review of the current submission: one, related to the proposed formulation of the drug product for marketing in the U.S.; the second, related to the manufacturing processes for the drug product. Regarding the former issue, the drug product used in the clinical trials consisted of a single dose, enclosed delivery system including a vial of triptorelin pamoate. the diluent (sterile water) and a sterile needle connected to a syringe. The sponsor proposes to market triptorelin pamoate in the U.S. as a vial alone, containing the lyophilized drug product. This product is to be reconstituted with sterile water using a 20-gauge needle. The sponsor provided *in-vitro* dissolution data to support the position that variations in the type of diluent or gauge and length of needle have minimal effect on the dissolution profile for the drug. These results were believed to support the position that variations in diluent, needle or syringe size would have minimal effect on drug effectiveness. However, since an *in-vitro/in-vivo* correlation has not been established for this product, variations in the bioavailability of the product when reconstituted with different diluents could not be assessed. Thus, use of sterile water as the only diluent for this product was incorporated into the label, thereby making the sponsor's proposal to market triptorelin pamoate in the U.S. as a vial alone is acceptable.

Regarding the second issue, the drug product was manufactured by the sponsor via two processes: one involving a [redacted] and one involving [redacted] During this review cycle, it was noted that the final products resulting from these different manufacturing processes were not bioequivalent, with a four-fold difference increase in AUC when manufactured by the [redacted] process. The

sponsor agreed to use the [redacted] manufacturing process for the to-be-marketed drug product and also agreed to dissolution specifications proposed by DRUDP.

Conclusions:

I agree with the conclusions of the primary and secondary reviewers that triptorelin pamoate is safe and effective for the palliative treatment of advanced prostate cancer and recommend approval of the product for this indication.

/S/ MD 5/29/00

Susan S. Allen, MD, MPH
Acting Director, HFD-580

Cc: NDA 20-715
Allen/Shames/Marks
Houn/Raczkowski/HFD-130

MAY 18 2000

Team Leader Memorandum

NDA 20-715
Complete Response to Non –Approvable letter of June 26,1997
Received: December 16, 1999
Memorandum Completed: May 17, 1999
Drug: Trelstar® Depot 3.75 mg (triptorelin pamoate)
Drug Class: GnRH agonist
Dose and Administration: 3.75 mg intramuscularly every one month
Indication: Palliative Treatment of Advanced Prostate Cancer
Sponsor: Debio Recherche Pharmaceutique S. A.
Martigny, Switzerland

Background: Triptorelin as the acetate or pamoate salt is marketed in over 60 countries for the treatment of advanced prostate cancer. The first approval was granted in Brazil in 1991. It subsequently won approval in Canada, Mexico, Europe and South America. [redacted] doses have been administered through 1997 and it has never been withdrawn. On June 24, 1996, The Division received NDA 20-715, Decapeptyl Depot (triptorelin pamoate), for monthly IM administration to patients for palliation of advanced prostate cancer. The submission consisted of three "core studies" with a total of 265 patients, comparing the ability of Decapeptyl and surgical orchiectomy to produce castrate levels of testosterone (T) in patients with advanced prostate cancer. The trials were conducted in England, Belgium and France between 1983 and 1989.

In each of the three studies, there were significant deficiencies in trial design, conduct, and data analysis. The sponsor's analysis of the primary efficacy variable (the ability to induce castrate levels of T in patients with advanced prostate cancer and maintain them) did not support the claim that Decapeptyl was effective for this indication. Due to inadequate and missing data, no definite conclusions about the safety of Decapeptyl could be reached.

Because of these deficiencies, the Division of Reproductive and Urologic Drug Products (hereafter referred to as The Division) found that Decapeptyl Depot was not approvable for the indication of palliative treatment of advanced prostate cancer. The application did not support the efficacy or safety of this drug.

At the time of the nonapprovable action, the sponsor was conducting trial DEB-96-TRI-01 which was designed to demonstrate the pharmacodynamic equivalence of the one-month and three month Depot preparations of Decapeptyl. The Division suggested to the sponsor that a study using an active controlled arm with an

approved GnRH agonist could satisfy the requirements for approval if safety and efficacy were demonstrated.

After the Division's suggestions, the sponsor discontinued enrolling patients into the Decapeptyl Depot 3-month arm of study DEB-96-TRI-01 and started enrolling patients to receive Lupron Depot 1-month in the comparator arm of the study. Approximately 140 patients had taken Decapeptyl Depot 1-month (now called Trelstar Depot 1-month) for 9 months when the comparator arm was changed. The portion of the study, DEB-96-TRI-01, that included 1-month triptorelin depot compared to 3-month triptorelin depot was called DEB-96-TRI-01 (first phase). This study was considered supportive for efficacy. The new study, which compared triptorelin 1-month depot to Lupron 1-month depot, was called DEB-96-TRI-01 (second phase). This trial was considered the primary efficacy study.

Conduct of the Trials:
DEB-96-TRI-01 was a parallel arm, randomized, open–label, active controlled, (triptorelin depot 3-month in the first phase and Lupron Depot 1-month in the second phase) multicenter study in men with advanced adenocarcinoma of the prostate. The triptorelin depot 1-month was administered IM every month for 9 months. Phase one of the trial was conducted in 19 centers in South Africa from Jan. 1997 to Sept. 1998. The second phase was also conducted in South Africa at 29 centers between Jan. 1998 and Feb. 1999.The co-primary efficacy endpoints were the rate of achieving castration (T< 1.735 nmol/L) by day 29 and the rate of maintaining castration from month 2 to 9. An important secondary endpoint was the avoidance of an LH surge (as a measure of acute-on-chronic flare) on reinjection at months 3 and 6.

Efficacy (DEB-96-TRI-01, second phase)
Achievement of Castration (second phase): The sponsor proposed to demonstrate "non-inferiority" between Lupron Depot 1-month and triptorelin depot 1-month during the second phase of DEB-96-01. The proposed lower bound of the confidence interval was not to exceed –10% with respect to the castration rate at 1 month between triptorelin and Lupron. All but one of 140 Lupron patients achieved castration on day 29 (99.3%) compared to 125 of 137 triptorelin patients (91.2%) The point estimate of the difference was –8% and the two sided confidence interval was (-15.7%, -1.4%). The sponsor therefore failed to make the predetermined non-inferiority endpoint for this study. It should be noted that of the 12 patients who took triptorelin that failed to achieve castration by day 29, 11 of them achieved castration by day 57 and all remained castrated through day 253.

The sponsor argues, correctly, that the castration achievement rate in the Lupron arm of the study was exceptionally high and that the point estimates for castration achievement rate for Lupron 1 month Depot in four phase-three studies used to support various Lupron approvals were 91%, 92%, 94% and 97%. The sponsor then calculated the achieve castration rate for triptorelin in patients for Deb-96-TRI-01

(both phases) and two smaller studies included in the submission. This "pooled" analysis revealed that three hundred and five of 332 patients achieved castrate levels of T by day 28 (91.9%). The sponsor then compared these results to the achieve castrate rate for Lupron Depot I-month that pooled the Lupron patients in DEB-96-TRI-01 and the four "historical control" studies. Three hundred and twenty one of 336 patients achieved castrate levels (95.5%). The difference in the point estimate was calculated to be –3.6% with the 95% confidence interval of (–9.2%, 0.1%). Thus achieving the predetermined non-inferiority test (-10% lower limit of confidence interval). I agree with the reviewer that this statistical approach is not appropriate. However, other analyses do support the efficacy of Trelstar with regard to achieving castration by one month.

Maintenance of Castration through Nine Months (second phase): In the triptorelin group, 132 of 137 (96.4%) of the patients remained in the castrate range for the entire nine months. In the Lupron arm, 128 of 140 patients (91.4%) remained castrate for the entire nine months.

Acute-on-Chronic Flare (second phase): The sponsor used an LH value of > 1.0 IU at 2 hours post reinjection as indicative of a flare. The primary reviewer and I find this acceptable in this study. Using this criterion, the triptorelin patients avoided a flare 98.4% of the time compared to 93.8% of the Lupron patients.

Efficacy (DEB-96-TRI-01, first phase)

Achievement of Castration (first phase): An analysis of the triptorelin 1-month depot arm of this study is considered supportive. Of 164 patients,152 achieved castration by day 29 (92.7%).

Maintenance of Castration (first phase): One hundred and fifty patients (including three that achieved castration by day 57) of 164 patients (94.2%) maintained castrate levels of castration for the nine months of the study.

"Acute-on-Chronic Flare"(first phase): The proportion of patients that avoided a flare as defined by a rise in LH above 1 IU at 2 hours post reinjection was 152 of 156 patients (97.4%)

Other studies

DEB-96-TRI-02 was a study of 32 patients on triptorelin 1-month depot lasting 2 months. Ninety–three percent achieved castration by day 29 and 100% by day 56.

DEB-98-TRI-01 was a trial of 13 patients on triptorelin 1-month depot that lasted 31 days. On day 29, 100 % of patients were castrate.

Safety of Triptorelin 1-month depot

The safety of triptorelin 1-month depot was satisfactorily demonstrated by the data submitted in the NDA, which included 350 patients that participated in the clinical trials. Hypersensitivity reactions are a concern in this class of products. There was no evidence of clinically significant hypersensitivity in th3e submitted trials. The sponsor provided a review of periodic safety update reports, which included immunogenic adverse events, reported overseas from1987 through 1997. During this period, approximately [redacted] vials of triptorelin were sold. Seven reports of angioedema, 3 reports of anaphylactic shock and 48 individual reports of rash, eczema, puritis, and allergy were reported.

The issue of immunoreactions is addressed in the **CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS,** sections of the label.

Other Relevant Issues

Chemistry: During the clinical trials, the sponsor used a Debioject or Debioclip delivery system which packaged the vials containing the triptorelin drug product, the diluent (sterile water), needle and syringe together for convenience. However after the trials were concluded, the sponsor decided [redacted] Therefore, they proposed to market the vial of Trelstar Depot (triptorelin pamoate) lyophilized power by itself and have the health care provider obtain the sterile water, syringe and needle.

The Division was initially concerned that variations in the amount and type of diluent needle and syringe size could effect the clinical effectiveness of Trelstar. In a response to The Division's concerns dated 10/1/99, the sponsor argued that it would be clearly stated in the label that 2ml of sterile water and a sterile 20-gauge needle should be utilized to prepare the drug product for patient use. The sponsor also offered data to prove that some variations in the type of diluent, volume of diluent, gauge and length of needle would probably have minimal effect drug effectiveness. This reviewer agrees with the sponsor's conclusions.

Both the chemistry and clinical reviewers believe that the **DOSAGE AND ADMINISTRATION** section of the Label adequately addresses the issue of drug reconstitution with the vial only configuration.

Assessment of Efficacy and Safety of Trelstar 1-Month Depot

The current standard for approval of GnRH agonists, that are 1 month depots used for the palliative treatment of prostate cancer, is the achievement of castration by one month and the maintenance of castration during a 3 month treatment phase. The success rates are compared to historical controls. Although Trelstar did not meet its predetermined statistical test for non-inferiority with the comparator, the primary reviewer and I believe that Trelstar demonstrated satisfactory efficacy in achieving castration with regard to historical controls (about 90% by one month).

In current standard trials for GnRH agonist 1-month depots, maintenance of castration is evaluated for 3 months. The sponsor evaluated Trelstar's ability to maintain castrate levels of T for nine months. The maintenance rate for Trelstar was 96.4% and 94.2% during the two large trials reported in this submission, compared to 91.2% for the Lupron arm. One could argue that the ability of drugs of this type to maintain castration is more important than the rapidity of achievement of castration when used for chronic therapy in patients with advanced cancer of the prostate. The acute-on-chronic flare rates were also comparable between Trelstar and the comparator.

I believe that the data from the trials contained in this submission also demonstrated safety comparable to other drugs in this class.

Recommendation
Therefore, I agree with the primary reviewer that Trelstar is safe and effective for palliative treatment of advance prostate cancer and should be approved for that purpose.

/S/

5/12/01

Daniel A. Shames MD
Team Leader, Urology
HFD-580, DRUDP
CDER/FDA

JUN 4 1997

Group Leader Memorandum

NDA:	**20-715**
Drug and indication:	**Decapeptyl® (triptorelin pamoate for depot suspension) for the palliative treatment of advanced prostatic cancer.**
Dose:	**one injection of 3.75 mg each month**
Applicant:	**Debio Recherche Pharmaceutique, S.A.**
Submission dated:	**June 24, 1996**
Date of MO review:	**May 16, 1997 (draft)**
Date of Memorandum:	**June 4, 1997**

In this application, the sponsor requests approval for a one-month depot formulation of triptorelin pamoate, an agonist analog of gonadotrophin releasing hormone, for the palliative treatment of advanced prostate cancer. In support of this indication, the sponsor has submitted the results of three studies conducted in the 1980's that compared the safety and efficacy of triptorelin with surgical castration. Based on discussions between the sponsor and this division, the primary evidence of efficacy was to be based on the demonstration of comparable levels of testosterone suppression between treatment groups.

I agree with the clinical reviewer's assessment that the clinical database is seriously deficient and that the sponsor's submission dated March 19, 1997, does not adequately address these deficiencies. Because of the problematic nature of this application, clinical and biopharmaceutics data were presented and discussed at CDER Scientific Rounds on April 10, 1997. I concur with the consensus of those attending this meeting, and with the recommendation of the primary reviewers that this application is not approvable.

The deficiencies from the clinical (including biometrics and DSI), biopharmaceutics, CMC and microbiological perspectives are detailed in the draft regulatory letter, and may be summarized as follows:

1. **Clinical:** The submitted data do not establish the safety or efficacy of triptorelin because of the high therapeutic failure rate in these studies and because of serious deficiencies in trial design and conduct (including lack of randomization, absence of a central laboratory, and inadequate follow-up and testosterone assessment).

2. **DSI:** Significant deficiencies at each of the four inspected sites included insufficient or non-existent documentation of randomization procedures; inadequate study records;

inadequate patient consent; and protocol violations in determining patient eligibility.

3. **Biopharmaceutics:** The clinical trials were not conducted with the to-be-marketed formulation and the submitted single-dose bioequivalence study does not support the bioequivalence of the clinical trial and the to-be-marketed formulations. Further, because only a single-dose study was conducted, there is insufficient data to determine the pharmacodynamic comparability of the two formulations.

4. **CMC/Microbiological:** Approvability issues concern the expiration dates of the drug product and numerous questions related to sterility assurance.

Following receipt of the action letter, the sponsor will be encouraged to meet with the division to discuss requirements for additional clinical development to support the safety and efficacy of triptorelin pamoate for the intended indication.

/S/

Heidi M. Jolson, M.D., M.P.H.
Deputy Division Director, HFD-580

cc:
NDA20-715
HFD-580/LRarick/DShames/HJolson

c:\h\20715.gl

Meeting Minutes

Date: May 17, 2000 **Time:** 12:00-1:00 pm **Location:** 17B-43

NDA 20-715 **Drug:** Trelstar® Depot 3.75 mg (triptorelin pamoate for injectable suspension)

Indication: Palliative treatment for advanced prostate cancer

Sponsor: Target Research Associates for Debio Recherche Pharmaceutique SA

Type of Meeting: Status/Labeling Meeting/OPDRA Preapproval Safety Conference

Meeting Chair: Dr. Susan Allen

Meeting Recorder: Ms. Jeanine Best

FDA Attendees:
Florence Houn, M.D., M.P.H., Director, Office of Drug Evaluation III (ODEIII, HFD-103)
Susan Allen, M.D., M.P.H., Acting Director, Division of Reproductive and Urologic Drug Products, (DRUDP, HFD-580)
Marianne Mann, M.D., Deputy Director, DRUDP (HFD-580)
Norman Marks, M.D., Medical Officer, DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D., Chemistry Team Leader, Division Of New Drug Chemistry II (DNDC II) @ DRUDP, (HFD-580)
Ameta Parekh, Ph.D., Phamacokintic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
David Lin, Ph.D., Chemist, DNDC II @ DRUDP (HFD-580)
Kathleen Uhl – Deputy Director, Office of Post Drug Review Assessment (OPDRA, DDRE2, HFD 440)
Denise Toyer, PharmD., Safety Evaluator, OPDRA (HFD-440)
Zili Li, Epidemiology Staff Fellow, OPDRA (HFD-440)
Mark Askine, Regulatory Reviewer, Division of Drug Marketing, Advertising, and Communications, (DDMAC, HFD-40)
Terri Rumble, B.S.N., Chief, Project Management Staff, DRUDP (HFD-580)
Jeanine Best, M.S.N., R.N., Regulatory Project Manager, DRUDP (HFD-580)

Meeting Objective: Final review status comments/OPDRA Preapproval Safety Conference

Background:
Trelstar® Depot 3.75 mg one-month intramuscular injection is a GnRH agonist that is a lyophilized biodegradable microgranule formulation supplied as a single-dose vial containing triptorelin pamoate, which forms a suspension when mixed with sterile water. This application is a complete response to the NA Action on June 26, 1997.

Discussion:
Chemistry:
- no approved USAN name for triptorelin pamoate; triptorelin is approved; sponsor to submit copy of USAN application and commitment to seek USAN approval for triptorelin pamoate

- recommended dissolution specifications accepted by sponsor
- sponsor has committed to using [redacted] only, in the manufacture of the drug product
- review is being finalized

Biopharmaceutics:
- review is being finalized

Pharmacology/Toxicology:
- not present

Biometrics:
- not present

Clinical:
- review is finalized; primary review with team leader for concurrence

OPDRA Preapproval Safety Conference:
- WHO database:
  - 1 case of anaphylaxis reported
  - 1 case of angioedema reported
  - 4 cases of increased SGPT; no liver function test elevations noted in clinical trials
  - most Adverse Reactions (AE's) are captured in the label, and reported AE's are not necessarily related to use of the drug product
  - will continue post-approval to monitor for hypersensitivity reactions, anaphylaxis, and angioedema
  -

draft

Labeling - DDMAC:
- comparison to Lupron has been removed from the label
- leave reference to use with hyperprolactinemic drugs in the **Drug Interactions** subsection; delete sentence [ ]
- in **Dose Adjustment** subsection,
  this was not studied
- in **Geriatric Use** subsection, safety and effectiveness claim in this age group has been removed

- **Decisions made:**
- Final reviews are to be completed by 9:00 am, May 19, 2000; following sign-off in Division, Action Package will be forwarded to the Office for sign-off

Action Items:
- J. Best to forward label deletion in **Drug Interactions** subsection to the sponsor today
- Final, signed-off reviews are due to J. Best by 9:00 am May 19, 2000; Action Package will circulate May 19 and May 22; to Susan Allen May 23, 2000

- Final reviews need to be entered in DFS before the Action Package is forwarded to the Office for sign-off

/S/

Minutes Preparer

/S/

Concurrence, Chair

5/23/00

cc:
Original NDA 20-715
HFD-580/DivFile
HFD-580/PM/Best
HFD-580/Allen/Mann/ /Marks/Rhee/Parekh/Lin/Rumble
HFD-103/Houn
HFD-440/Uhl/Toyer/Li
HFD-40/Askine
drafted:JAB/May 17 2000/NDA20715mtg051700.doc
concurrence: Allen,05.17.00/Mann, 05.17.00/Uhl,05,17.00/Toyer,05.18.00/Houn, 05.18.00/Lin.05.19.00/
Rhee,05.19.00/Rumble,05.22.00
final: JAB/May 22, 2000
MEETING MINUTES

Meeting Minutes

Date: May 1, 2000 **Time:** 12:00-1:00 pm **Location:** 17B-43

NDA 20-715 **Drug:** Trelstar® Depot 3.75 mg (triptorelin pamoate for injectable suspension)

Indication: Palliative treatment for advanced prostate cancer

Sponsor: Target Research Associates for Debio Recherche Pharmaceutique SA

Type of Meeting: Status/Labeling Meeting

Meeting Chair: Dr. Marianne Mann, M.D.

Meeting Recorder: Ms. Jeanine Best

FDA Attendees:
Susan Allen, M.D., M.P.H., Acting Director, Division of Reproductive and Urologic Drug Products, (DRUDP, HFD-580)
Marianne Mann, M.D., Deputy Director, DRUDP (HFD-580)
Daniel Shames, M.D., Team Leader, DRUDP (HFD-580)
Norman Marks, M.D., Medical Officer, DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D., Chemistry Team Leader, Division Of New Drug Chemistry II (DNDC II) @ DRUDP, (HFD-580)
Ameta Parekh, Ph.D., Phamacokintic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
David Lin, Ph.D., Chemist, DNDC II @ DRUDP (HFD-580)
Krishan Raheja, D.V., Ph.D., Pharmacologist, DRUDP (HFD-580)
David Hoberman, Ph.D., Statistician, DB II @ DRUDP (HFD-580)
Terri Rumble, B.S.N., Chief, Project Management Staff, DRUDP (HFD-580)
Jeanine Best, M.S.N., R.N., Regulatory Project Manager, DRUDP (HFD-580)

Meeting Objective: To discuss status of reviews and approvability of the application, and finalize initial labeling comments for sponsor.

Background:
Trelstar® Depot 3.75 mg one-month intramuscular injection is a GnRH agonist that is a lyophilized biodegradable microgranule formulation supplied as a single-dose vial containing triptorelin pamoate, which forms a suspension when mixed with sterile water. This application is a complete response to the NA Action on June 26, 1997.

Discussion:
Chemistry:
- teleconference with sponsor on 4/20/00, discussed manufacturing processes and dissolution specifications:

- drug product is manufactured by two processes [redacted]; final products from these two processes are not bioequivalent, and act differently pharmacokinetically with a four-fold difference in the AUC; Division recommended use of [redacted] to manufacture the drug product; even if the sponsor withdraws the batches from the NDA which were manufactured by the [redacted], there are adequate number of batches made by the [redacted] being used in the clinical studies and stability studies to support approval
- four sets of data from batches made by the [redacted] are provided to establish *in vitro* dissolution specifications; three sets were analyzed with a method that uses [redacted] for quantitating the standard, and one set was analyzed with [redacted] for quantitating the standard (more accurate)

- provided the sponsor two weeks to respond to the above issues
- The quantitative composition of the individual vials is not proportional to the quantitative composition of the ful scale batch; is the unused portion discarded?; will confirm with the sponsor
- review is nearing completion
- initial electronic labeling revisions are complete

Biopharmaceutics:
- dissolution specification concerns as listed above in Chemistry section
- draft review complete
- will complete initial electronic labeling revisions today

Pharmacology/Toxicology:
- no concerns
- review is nearing completion
- initial electronic labeling revisions are complete

Biometrics:
- review is complete; results of analysis given to N. Marks and M. Mann; mainly descriptive statistics

Clinical:
- review is in rough draft format
- initial electronic labeling revisions are complete
- have OPDRA watch for severe hypersensitivity reactions

Labeling:
- minor editorial and word changes were made
- Draft
- deleted information regarding efficacy outcomes of this product as compared to other GnRH agonists; difficult to define similarity
- requested sponsor to re-design AE Table as done in the Viadur® label
- repeat statement regarding hypersensitivity reactions in **WARNINGS** section
- **OVERDOSAGE** section; no overdoses in clinical trials; effects of overdosage unknown

- **Decisions made:**
- Final reviews and negotiations are to be completed by May 23, 2000; following sign-off in Division, Action Package will be forwarded to the Office for sign-off

Action Items:

- J. Best to forward initial label revisions to the sponsor by COB today
- J. Best to follow-up with outstanding Microbiology consult and OPDRA tradename consult
- J. Best to request mock-ups from sponsor of all packaging materials for D.Lin's review
- D. Lin to discuss difference in size between full scale batch and amount of product in vials with a Debio chemist on 5/2/00

/S/

Minutes Preparer

/S/ M.D. 5/10/00

Concurrence, Chair

cc:
Original NDA 20-715
HFD-580/DivFile
HFD-580/PM/Best
HFD-580/Allen/Mann/Shames/Marks/i/Rhee/Parekh/Lin/Hoberman/Raheja/Rumble
drafted:JAB/May 2, 2000/N20715STATLABmtg050100.doc
concurrence: Mann,05.02.00/Shames,05.02.00/Rhee,05.02.00/Lin,05.04.00/Allen,05.05.00
final: JAB/May 10, 2000
MEETING MINUTES

Teleconference Meeting Minutes

Date: April 20, 2000 **Time:** 11:30 am -12:05 pm **Location:** Parklawn; 17B-45

NDA 20-715 **Drug:** Trelstar® Depot 3.75 mg (triptorelin pamoate for injectable suspension)

Indication: Palliative treatment for advanced prostate cancer

Sponsor: Target Research Associates for Debio Recherche Pharmaceutique SA

Type of Meeting: Teleconference for Chemistry/Biopharmaceutical Issues

Meeting Chair: Dr. Marianne Mann

Meeting Recorder: Ms. Jeanine Best

FDA Attendees:
Marianne Mann, M.D., Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP, HFD-580)
John Hunt, Ph.D., Deputy Director, Division of Pharmaceutical Evaluation II (DPE II, HFD-870)
Moo-Jhong Rhee, Ph.D., Chemistry Team Leader, Division Of New Drug Chemistry II (DNDC II) @ DRUDP, (HFD-580)
Ameta Parekh, Ph.D., Phamacokintic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
David Lin, Ph.D., Chemist, DNDC II @ DRUDP (HFD-580)
Soraya Madani, Ph.D., Pharmacokinetics Reviewer, OCPB @ DMEDP (HFD-510)
Jeanine Best, M.S.N., R.N., Regulatory Project Manager, DRUDP (HFD-580)

External Participants:
Target Research:
Jill Powers
Robert McCormack
Debiopharm:
Pierre Grosgurin
Herve Porchet
Myriam Weiner
Debio RP:
Christian George
Piero Orsolini
Evelyn Vuaridel
Consultant:
[redacted]

Meeting Objective: To discuss Chemistry and Biopharmaceutical issues necessary for resolution to move ahead for Action on this NDA.

Discussion:
Issue # 1:

- [redacted] are used in the manufacture of the drug product, [redacted] and [redacted]
- The batches produced by the [redacted] have different *in vitro* release profiles, and the Division does not find bioequivalence between the batches upon cross-study comparison
- The Division finds that the batches produced by [redacted] (batch used in study Deb-95-TRI-02) are not acceptable for the drug product in this NDA; the [redacted] procedure has a four-fold increase in the systemic exposure with the same testosterone response as compared to the batches produces by [redacted] drug products must be consistent and of the same quality
- Sponsor may choose to market batches made by [redacted] alone, or can establish bioequivalence between batches by performing a traditional bioequivalence study using a crossover trial in the same patient population

Issue # 2:

- Four sets of data from batches made by the [redacted] are provided to establish *in vitro* dissolution specifications; three sets were analyzed with a method that uses [redacted] for quantitating the standard, and one set was analyzed with [redacted] for quantitating the standard (more accurate)
- Division requests that dissolution specifications be set based on the [redacted] analysis method; ± 10% of the mean numbers

Decisions made:
Issue # 1:

- Sponsor will manufacture the to-be-marketed drug product with the [redacted] only

Issue # 2:

- Sponsor will analyze the batches with both methods to establish linkage; 72 hours are required to perform analyses; this data should be available for the Division in two weeks; if the data is not submitted within the next 2 weeks, FDA will use the mean data from batch # D601D01K7 and set specifications ± 10% of the mean values

Action Items:

- J. Best will remind the sponsor that the Action date is rapidly approaching and that Action Package needs to be finalized by May 23, 2000, in order to go to the Office for sign-off

/S/
Minutes Preparer

/S/ MD
Concurrence, Chair
4/28/00

Note to Sponsor:
These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

cc:
Original IND
HFD-580/DivFile
HFD-580/PM/Best
HFD-580/Mann/Rhee/Parekh/Lin
HFD-510/Madani
HFD-870/Hunt

drafted: JAB/April 20, 2000/N20715TCON042000.doc
concurrence: Rhee,04.20.00/Madani,04.20.00/Mann,04.21.00/Lin,04.24.00/Rumble,04.25.00
no concurrence received: Parekh/Hunt
final: JAB/April 28, 2000

MEETING MINUTES

Meeting Minutes

Date: April 5, 2000 **Time:** 1:00-2:00 pm **Location:** 17B-43

NDA 20-715 **Drug:** Trelstar® Depot 3.75 mg (triptorelin pamoate for injectable suspension)

Indication: Palliative treatment for advanced prostate cancer

Sponsor: Target Research Associates for Debio Recherche Pharmaceutique SA

Type of Meeting: Status/Labeling Meeting

Meeting Chair: Dr. Marianne Mann, M.D.

Meeting Recorder: Ms. Jeanine Best

FDA Attendees:
Marianne Mann, M.D., Deputy Director, DRUDP (HFD-580)
Daniel Shames, M.D., Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP, HFD-580)
Norman Marks, M.D., Medical Officer, DRUDP, (HFD-580)
Moo-Jhong Rhee, Ph.D., Chemistry Team Leader, Division Of New Drug Chemistry II (DNDC II) @ DRUDP, (HFD-580)
Ameta Parekh, Ph.D., Phamacokintic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
David Lin, Ph.D., Chemist, DNDC II @ DRUDP (HFD-580)
Soraya Madani, Ph.D., Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)
Krishan Raheja, D.V., Ph.D., Pharmacologist, DRUDP (HFD-580)
David Hoberman, Ph.D., Statistician, DB II @ DRUDP (HFD-580)
Jeanine Best, M.S.N., R.N., Regulatory Project Manager, DRUDP (HFD-580)

Meeting Objective: To discuss status of reviews and approvability of the application, and to inform review team of Action Goal Dates.

Background:
Trelstar® Depot 3.75 mg one-month intramuscular injection is a GnRH agonist that is a lyophilized biodegradable microgranule formulation supplied as a single-dose vial containing triptorelin pamoate, which forms a suspension when mixed with sterile water. This application is a complete response to the NA Action on June 26, 1997.

Discussion:
Chemistry:
- Major issue is the [redacted]-year expiration date that the sponsor is seeking; inadequate stability data has been provided to support proposed expiration date; in addition the sponsor is requesting loosened specifications; full stability studies were not performed

- Major stability issue involves sponsor using [redacted] to manufacture the drug product; batches produced with [redacted] have different release profiles; no IV/IVC is established to link between batches produced by the [redacted] sponsor proposes to link products based on *in vivo* data suggesting comparable PK levels in two separate groups of patients
  - [redacted] provided the drug product for the clinical trials, while the [redacted] provided the drug product for stability testing; both products are therefore, pivotal to the application
- Sponsor has responded to chemistry issues raised in NDA [redacted] by submitting them to this NDA; although not required for this NDA, relevant information will be reviewed
- Sponsor has been using two established names interchangeably: "triptorelin pamoate for depot suspension" and "triptorelin pamoate for injectable suspension"; the acceptable established name is "triptorelin pamoate for injectable suspension
- Site inspections are complete and acceptable

Biopharmaceutics:

- The two products must be comparable *in vivo* to support sponsor's contention that the *in vitro* differences do not matter
- Traditional bioequivalence studies were not performed between slow release and fast release batches; have not directly established *in vivo* correlation; sponsor claims they compared PK profiles using the same drug product with two different in vitro release characteristics in two different patient populations and the PK profiles seem comparable; this will be carefully reviewed by Biopharm
- *In vitro* dissolution specifications need further review by both Chemistry and Biopharm reviewers

Pharmacology/Toxicology:

- Animal drug dosing should be expressed in multiples of the human therapeutic dose either on systemic exposure or on body surface area basis; this can be addressed in labeling

Biometrics:

- Data handling and statistics are confusing, have spoken with sponsor's statistician and will obtain clarification
- Need to ascertain if failures were counted in analysis; and if missing patients were counted as failures; the reason for drop-outs, i.e., lack of suppression of testosterone, is unclear
- Sponsor performed maintenance analysis from Day 57 until end, instead of Day 29 until end of trial; FDA will analyze from Day 29 until end of trial
- Suppression to castrate levels by Day 28 was 91.2 % in the ITT population, with 6 patients missing; Lower boundary of the confidence interval should be 10% but was noted to be 15.9%; cannot determine if maintenance was achieved until the end of the trial; require more information, including a month to month break-down of the data; could be pivotal to support approvability, remains a review issue

Clinical:

- Endpoints used for analysis are the current acceptable endpoints recommended for prostate cancer trials
- Historical comparison used Lupron
- Currently looking at drop-out data and its effect on efficacy and safety

- Conclusion: appears to be that triptorelin did not work as quickly as Lupron an achieving castrate levels; therefore, we must be comfortable with maintenance data for approval

- **Decisions made:**
- Final reviews and negotiations are to be completed by May 23, 2000; following sign-off in Division, Action Package will be forwarded to the Office for sign-off
- Electronic labeling is available on the "N" Drive; initial label revisions to be completed by COB 4/19/00

Action Items:
- J. Best to forward label revisions to the sponsor on or about 4/20/00
- Biopharm team will address IV/IVC concerns with John Hunt to see if DRUDP can accept two different manufacturers of the drug product based on the existing data
- Sponsor will be requested to submit appropriate data and statistics for analysis

/S/ mrw rw
Minutes Preparer

/S/ MD
Concurrence, Chair
4/14/00

cc:
Original NDA 20-715
HFD-580/DivFile
HFD-580/PM/Best
HFD-580/Mann/Shames/Marks/Madani/Rhee/Parekh/Lin/Hoberman/Raheja
drafted:JAB/April 6, 2000/N20715SLmtg040500.doc
concurrence:Rhee,04.06.00/Madani,04.06.00/Raheja,04.06.00/Shames,04.06.00/Mann,04.07.00/Rumble, 04.07.00
concurrence not received: Marks/Parekh/Lin/Hoberman
final: JAB/April 14, 2000
MEETING MINUTES

Meeting Minutes

Date: January 19, 2000 **Time:** 11:00-11:30 am **Location:** 17B-43

NDA 20-715 **Drug:** Trelstar® Depot 3.75 mg (triptorelin pamoate for depot suspension)

Indication: Palliative treatment for advanced prostate cancer

Sponsor: Target Research Associates for Debio Recherche Pharmaceutique SA

Type of Meeting: Internal/Determination of complete response to 6/26/97 NA action letter

Meeting Chair: Dr. Dan Shames, M.D.

Meeting Recorder: Ms. Jeanine Best

FDA Attendees:
Susan Allen, M.D., M.P.H., Acting Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Marianne Mann, M.D., Deputy Director, DRUDP (HFD-580)
Daniel Shames, M.D., Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP, HFD-580)
Shelley Slaughter, M.D., Ph.D., Team Leader, DRUDP (HFD-5800
Norman Marks, M.D., Medical Officer, DRUDP, (HFD-580)
Moo-Jhong Rhee, Ph.D., Chemistry Team Leader, Division Of New Drug Chemistry II (DNDC II) @ DRUDP, (HFD-580)
Ameta Parekh, Ph.D., Phamacokintic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
David Lin, Ph.D., Chemist, DNDC II @ DRUDP (HFD-580)
Soraya Madani, Ph.D., Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)
David Hoberman, Ph.D., Statistician, DB II @ DRUDP (HFD-580)
Terri Rumble, B.S.N., Chief, Project Management Staff, DRUDP (HFD-580)
Jeanine Best, M.S.N., R.N., Regulatory Project Manager, DRUDP (HFD-580)

Meeting Objective: To determine if the sponsor's December 16, 1999 resubmission is a complete response to the June 26, 1997 NA action letter that outlined CMC and Clinical deficiencies, and noted relevant CMC, Biopharmaceutic, and Microbiology issues.

Background:
Trelstar® Depot 3.75 mg one-month intramuscular injection is a GnRH agonist that is a lyophilized biodegradable microgranule formulation supplied as a single-dose vial containing triptorelin pamoate, which forms a suspension when mixed with sterile water.

Discussion:
Clinical:
- One clinical trial repeated using the Debioject, not the vial alone product; clinical trial was conducted to demonstrate the achievement and maintenance of castration

- Sponsor intends to market the vial alone product; provider to mix with sterile water prior to injecting
- Sponsor performed chemistry bench tests to demonstrate that different solutions or needle size do not affect the amount of drug product delivered
- Suspensibility is similar to Lupron; if particle size is similar to Lupron, results should be acceptable; particle size affects suspensibilty; must give injection when mixed, before precipitate occurs

Chemistry:
- Stability data should be similar for the vial alone versus the combination product that was used in the Clinical Trials.
-
- Reinspection of facilities will be required due to time lapse since last inspections
- A Microbiology consult is required since this is an injectable product
- Sponsor must verify that a copy of the submission was sent to field office for review

Biopharmaceutics:
- Sponsor submitted both one-month and three-month formulation data; we will look at one-month data only in this NDA, since this a response to a NA action for the one-month product formulation
- Require data on *in vitro* dissolution studies using the new clinical batches

Statistics:
- Cannot ascertain from the Clinical Trial data if the patients enrolled in the Phase 2 study were new (naïve) patients or if they were the same patients that were used in the comparitor trial with Lupron

Pharmacology/Toxicology:
- Not represented at this meeting; no NA issues were identified during initial review

Decisions made:
- This submission is determined to be a complete response to the June 26, 1997 NA action and will be reviewed
- Review is on a six-month time-line; and, because the product is an NME, Office sign-off is required
- Reviews need to be completed by early May in order to forward Action Package to the Office on May 16, 2000; action date is June 16, 2000

Action Items:
- J. Best to request Microbiology consult
- J. Best to request DSI inspections; N. Marks to choose two sites for DSI inspection audit
- D. Lin to determine the particle size of Lupron for comparison purposes
- J. Best to request sponsor to respond to questions that arose during this meeting
- J. Best to inform Sponsor that only the one-month formulation data will be looked at in this NDA; the sponsor can submit another NDA at this time with the three-month formulation data (full user fee), or they can submit a supplement after this product is approved (one-half user fee)

/S/

Minutes Preparer

/S/

Concurrence, Chair

ADDENDUM:
Subsequent to the filing meeting it was decided that a separate NDA is required for the 3-month formulation drug product because the formulations differ for the 1 and 3-month products. This information was relayed to the sponsor.

cc:
Original IND
HFD-580/DivFile
HFD-580/PM/Best
HFD-580 Allen/Mann/Shames/Marks/Madanis/Rheem/Prekh/Lin/Hoberman/Rumble

drafted:JAB/January 20,2000/N20715filmtg011900.doc
concurrence:Mann,01.20.00/Allen,01.20.00/Rhee,01.20.00/Madani,01.20.00/Lin,01.20.00/
Rumble,01.20.00
final:JAB/January 27, 2000

MEETING MINUTES

Meeting Minutes

Date: June 8, 1999 **Time:** 1:00-2:00 PM. EDT **Location:** Parklawn, Potomac Room

NDA 20-715 **Drug:** Decapeptyl (triptorelin)

Indication: GNRH-agonist for prostate cancer

Sponsor: Debio Recherche Pharmaceutique SA

Type of Meeting: Pre-NDA (resubmission)

Meeting Chair: Marianne Mann, MD

External Lead: Robert McCormack, PhD

Meeting Recorder: Kim Colangelo, BS

FDA Attendees:
Florence Houn, MD – Director, Office of Drug Evaluation III (ODE III; HFD-103)
Marianne Mann, MD – Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Dan Shames, MD – Urology Team Leader, DRUDP (HFD-580)
Norman Marks, MD – Urologist, Medical Officer, DRUDP (HFD-580)
John Gibbs, PhD – Director, Division of New Drug Chemistry II (DNDC II; HFD-820)
Moo-Jhong Rhee, Ph.D., Chemistry Team Leader, DNDC II @ DRUDP (HFD-580)
David Lin, Ph.D., Chemistry Reviewer, DNDC II @ DRUDP (HFD-580)
Neil Sweeney, PhD – Microbiologist, Office of New Drug Chemistry (ONDC; HFD-805)
Ameeta Parekh, Ph.D., Team Leader, Division of Pharmaceutical Evaluation II (DPE II) @ DRUDP (HFD-580)
Soraya Madani, Ph.D., Clinical Pharmacology and Biopharmaceutics Reviewer, DPE II @ DRUDP (HFD-580)
Lisa Kammerman, PhD – Statistics Team Leader, Division of Biometrics II (DB II) @ DRUDP (HFD-580)
Terri Rumble, BSN – Chief, Project Management Staff, DRUDP (HFD-580)
Eufrecina DeGuia – Regulatory Project Manager, DRUDP (HFD-580)
Kim Colangelo, BS – Regulatory Project Manager, DRUDP (HFD-580)

External Attendees:
Hervé Porchet, MD – Director, Clinical Pharmacology, Debiopharm
Robert McCormack, PhD - Regulatory Affairs
Pierre Grosgurin, MSc – Manager, Biostatistics and Clinical Data, Debiopharm
Myriam Weiner, PharmD – Project Manager, Debiopharm
Beryl Asp, PhD, Clinical Development, Pharmacia & Upjohn
Daniel Mannix, PhD - Pharmacia & Upjohn
Piero Orsolini, PhD – President and Chief Executive Officer, Debio R.P.
Christian George, PhD – Director, Quality Assurance, Debiopharm

Meeting Objective: To ensure the adequacy of the content and format of Debio's complete response to the non-approvable (NA) letter sent June 26, 1997.

Background: Chemistry, Microbiology and Biopharmaceutical information submitted in response to the NA letter was submitted February 11, 1999; the Clinical and Statistical information is scheduled for submission in the third quarter of 1999; this product is currently under review for [redacted] (NDA [redacted]).

Discussion:

- meeting package submitted May 10, 1999 (questions listed in overheads); overheads presented at the meeting are attached
- response to clinical question #1: adequacy will be determined during the review of the data; information included appears to be acceptable for filing; the review will address DRUDP's concern with the comparison to Lupron (results demonstrated Lupron was quicker to achieve effect); the long-term administration of this product will be considered in the review
- response to clinical question #3: study data in the Integrated Summary of Safety should be presented both pooled and separately (for previous submission and current studies)
- the Kaplan-Meier curves of maintenance of castration levels from Months 2 through 9 (patients escape castration as an event) will be included in the submission
- an analysis in which the denominator stays constant for missing data (e.g., p. 27, line 1) should be included in the submission
- Debio agreed to calculate two-sided 95% confidence intervals for the differences between decapeptyl and Lupron
- response to clinical question #4: two guidance documents regarding electronic submissions are available on the Internet (www.fda.gov\cder)
- response to biopharmaceutics questions:
  - the information provided appears sufficient for filing
  - dissolution issues from [redacted] apply to this submission: specifications should be set to reach plateau of [redacted]% dissolution; Debio responded that surfactants and other solvents have been researched, and the information was submitted February 19, 1999, to NDA 21-002
  - *in vivo-in vitro* correlation (IVIC): reanalysis is recommended to show percent absorbed vs. percent dissolved *in vitro*; the analysis as provided is difficult to interpret
  - information is needed to show how to predict the *in vivo* data (C_{max} and AUC) based on the proposed lower and upper specifications, as well as how the specifications are obtained from *in vivo* studies
  - whenever possible, the reviews will be harmonized; however, the NDAs will be officially handled as two separate applications
- response to manufacturing/quality control question #1: additional packaging configurations should be submitted via a supplement because the submission should be limited to the responses to the NA letter; [redacted], Debio asserted that the vial is part of the package (Debioject) submitted in this NDA
- response to manufacturing/quality control question #2: chemistry information provided appears to be acceptable for filing
- response to manufacturing/quality control question #3: Debio reported that they were reverting to the [redacted] because [redacted]; Debio reported that stability data for [redacted] was

included in the original NDA submission, but may not have been clearly identified; DRUDP noted that the ratios of polymer/peptide are different, which will need to be assessed in the review

- response to manufacturing/quality control question #4: DRUDP recommended post-approval submission of a supplement for new suppliers
- response to manufacturing/quality control question #5: a new facility can be added to the NDA, via a supplement after approval;
- response to manufacturing/quality control question #6: the same reviewer is reviewing both NDAs
- response to microbiology question #1: acceptable, but it should be noted that the Debioject will require media fill validation for that assembly
- response to microbiology question #2: acceptable
- response to Decapeptyl 3-Month formulation question #1: the 3-month depot cannot be submitted as proposed until the 1-month depot is approved, unless submitted as a stand-alone, separate NDA

Decisions made:

- data appears to be sufficient for filing
- information to be submitted:
  - study data in the Integrated Summary of Safety presented both pooled and separately (previous submission and current studies)
  - the Kaplan-Meier curves of maintenance of castration levels from Months 2 through 9
  - an analysis in which the denominator stays constant for missing data (e.g., p. 27, line 1)
  - two-sided 95% confidence intervals analysis for the differences between decapeptyl and Lupron
  - information to show how to predict the *in vivo* data (C_{max} and AUC) based on the proposed lower and upper specifications
- new data cannot be submitted until after approval (

Unresolved decisions:

- inclusion of vial alone in NDA 20-715 for review

Action Items:

- Debio to submit rationale for inclusion of vial (i.e., not new data) in resubmission to NDA 20-715 *[Note: following additional internal discussion, Dr. McCormack was informed via telephone on June 10, that the vial will not be accepted in this submission (response to a not approvable letter) since additional stability data would be needed; on June 11, 1999, Dr. McCormack contacted DRUDP to inform that the rationale for including the vial package configuration would nonetheless still be submitted]*
- minutes will be provided to the sponsor within 30 days

/S/

Minutes Preparer

/S/ M.D.

Concurrence, Chair

7-1-99

cc:
Original NDA 20-715
HFD-580/DivFile
HFD-580/Colangelo/Rumble
HFD-580/Rarick/Mann/Shames/Rhee/Lin/Parekh/Madani/Kammerman
HFD-820/Gibbs
HFD-805/Sweeney

drafted: Colangelo, 06.20.99
concurrence: Mann, Parekh, Marks, Lin, Kammerman, 06.21.99; DeGuia, Rhee, Rumble, 06.22.99; Madani, 06.23.99; Shames, 06.25.99
final:

MEETING MINUTES

Summary of Data on Testosterone Suppression (≤1.735 nmol/L)					
Data from Leuprolide Regulatory File & Study DEB-96-TRI-01 (PP Population)			Data from Triptorelin Pamoate Studies (PP Population)		
	Percent (#) Patients Castrated			Percent (#) Patients Castrated	
Study	By Week 4	By Week 8	Study	By Week 4	By Week 8
DEB-96-TRI-01 2nd phase	99% (136/137)	97% (131/135)	DEB-96-TRI-01 2nd phase[c]	91% (123/135)	98% (126/129)
M93-013	94% (46/49)	100% (49/49)	DEB-96-TRI-01 1st phase[d]	92% (152/164)	99% (156/158)
M91-583	92% (56/61)	97% (59/61)[a]	DEB-96-TRI-02	93% (28/30)	100% (30/30)
M91-653	97% (32/33)	97% (32/33)[b]	DEB-98-TRI-01	100% (13/13)	N/A
M85-097	91% (51/56)	95% (53/56)[c]			
Overall	95% (321/336)	97% (324/334)	Overall	92% (316/342)	98% (312/317)

[a] Onset of castrate testosterone levels for remaining two patients by weeks 15 and 28
[b] One patient unable to reach suppression due to death on day 6
[c] Onset of castrate testosterone levels by one patient by day 66 and two patients unable to reach suppression due to not having data beyond day 4 and week 2
[d] Patients in 1-month triptorelin arm from comparison of 3-month vs. 1-month triptorelin
[e] Patients in 1-month triptorelin arm from comparison of triptorelin vs. leuprolide 1-month formulations

Summary of "Escape" Incidents in Study DEB-96-TRI-01 (PP Population)		
	Triptorelin	Leuprolide
Total subjects	135 (100%)	137 (100%)
Subjects achieving castration by week 8	134 (99%)	136 (99%)
Castrated subjects with escapes (not due to missing scheduled drug injections)	4/134 (2.9%)	8/133 (6.0%)[a]

[a] Three subjects in leuprolide group had escapes following missing or late scheduled injections