CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-715

Approval Letter

Food and Drug Administration
Rockville MD 20857

JUN 15 2000

NDA 20-715

Debio Recherche Pharmaceutique S.A.
C/O Target Research Associates
Attention: Robert J. McCormack, Ph.D.
Vice President, Regulatory Affairs
554 Central Avenue
New Providence, NJ 07974

Dear Dr. McCormack:

Please refer to your new drug application (NDA) dated December 16, 1999, received December 16, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Trelstar™ Depot (triptorelin pamoate for suspension injection).

We acknowledge receipt of your submissions dated July 3 and November 10, 1997, February 11, March 30, April 13, May 10 and 26, September 21, November 10 and December 16, 1999, February 1, 8, 14, 17 and 22, March 15, 27 and 30, April 4, 5, 17, 18 (2), 24 (2) and 25, May 5, 9, 11 (2), 15, 19, 22 and 23, June 5, 8, 12, 13 and 15, 2000. Your submission of December 16, 2000 constituted a complete response to our June 26, 1997 action letter.

This new drug application provides for the use of Trelstar™ Depot (triptorelin pamoate for suspension injection) for the palliative treatment of advanced prostate cancer.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert faxed June 15, 2000, immediate container and carton labels submitted June 12, 2000). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 20-715." Approval of this submission by FDA is not required before the labeling is used.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you have not fulfilled the requirements of 21 CFR 314.55 (or 601.27). We are deferring submission of your pediatric studies until 12/2/00. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

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

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

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Reproductive and Urologic Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Jeanine Best, M.S.N., R.N., Regulatory Project Manager, at (301) 827-4260.

Sincerely,

/S/

Florence Houn, M.D., M.P.H., F.A.C.P.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Archival NDA 20-715
HFD-580/Div. Files
HFD-580/J.Best
HFD-580/Allen/Mann/Shames/Marks/Rhee/Lin/Parekh/Jordan/Raheja/Kammerman/Hoberman
HFD-103/Houn
HFD-510-Madani
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-103/ADRA (with labeling)
HFD-102/Post-Marketing PM
HFD-104/Peds/V.Kao (with labeling)
HFD-104/Peds/T.Crescenzi (with labeling)
HFD-40/DDMAC (with labeling)
HFI-20/Press Office (with labeling)
HFD-400/OPDRA (with labeling)
HFD-613/OGD (with labeling)
HFD-095/DDMS-IMT (with labeling)
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: JAB/May 19, 2000
final: JAB/June 15, 2000
filename: N20715Apltr0500.doc

APPROVAL (AP) (with Phase 4 (pediatric) Commitments)

NAME	SIGNATURE
Florence Houn, M.D., M.P.H. Director Office of Drug Evaluation III (ODE III, HFD-103)	6/13/00
Susan Allen, M.D. M.P.H. Acting Director Division of Reproductive and Urologic Drug Products (DRUDP, HFD-580)	6/2/00
Daniel Shames, M.D. Urology Team Leader DRUDP (HFD-580)	5/19/00
Norman Marks, M.D. Medical Officer DRUDP (HFD-580)	M.D. 5/19/00
David Morse, Ph.D. Pharmacology Team Leader Division of Anti-Viral Drug Products (DAADP, HFD-530)	6/15/00
Alexander Jordan, Ph.D Pharmacology Team Leader DRUDP (HFD-580)	5/22/00
Krishan Raheja, D.V.M., Ph.D Pharmacologist DRUDP (HFD-580)	5/19/00
John Gibbs, Ph.D Director Division of New Drug Chemistry II (DNDC II, HFD-820)	6/15/00
Moo-Jhong Rhee, Ph.D. Chemistry Team Leader Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)	5/19/00
David Lin, Ph.D. Chemist DNDC II @ DRUDP (HFD-580)	5/19/00
Ameeta Parekh, Ph.D. Pharmacokinetic Team Leader Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)	5/19/00
Soraya Madani, Ph.D. Pharmacokinetics Reviewer OCPB @ DRUDP (HFD-580)	5/19/00

NDA 20-715
Trelstar®
Debio Recherche Pharmaceutique S.A.

Ed Nevius, Ph.D. Director Division of Biometrics II (DB II, HFD-715)	[redacted] 5/19/00
Lisa Kammerman, Ph.D Biometrics Team Leader Division of Biometrics II (DB II) @ DRUDP (HFD-580)	[redacted] 5/19/00
David Hoberman, Ph.D.. Statistician DB II @ DRUDP (HFD-580)	[redacted] 5/19/00
Peter Cooney, Ph.D. Microbiology Team Leader DNDC (HFD-160)	[redacted] for [redacted] 5/19/2000
David Hussong, Ph.D. Microbiologist DNDC (HFD-160)	[redacted] 5/19/2000
Terri Rumble, B.S.N. Chief, Project Management Staff DRUDP (HFD-580)	[redacted] 5/19/00
Jeanine Best, M.S.N., R.N. Regulatory Project Manager DRUDP (HFD-580)	[redacted] 5/19/00
Marianne Mann, M.D. Deputy Director DRUDP (HFD-580)	[redacted] 05/31/00

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-715

Approvable Letter

Food and Drug Administration
Rockville MD 20857

NDA 20-715

Kostopulous & Associates
Attention: Mr. N. Peter Kostopulous
1747 Pennsylvania Ave., N.W., Suite 300
Washington, D.C. 20006

JUN 26 1997

Dear Mr. Kostopulous:

Please refer to your new drug application dated June 24, 1996, received June 26, 1996, submitted on behalf of Debio Recherche Pharmaceutique, S.A., under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Decapeptyl® (triptorelin pamoate for depot suspension) Depot.

We acknowledge receipt of your submissions dated July 9 (2), September 6, 12, 19, and 27, October 15, November 19, and December 10, 1996; and January 10, 23, 27, 30, and 31, February 7 (2) and 26, and March 14, 19, 26, and 27, 1997. The User Fee goal date for this application is June 26, 1997.

We have completed our review and find the information presented is inadequate, and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows:

Clinical

From the clinical perspective, this application is not approvable because of significant deficiencies in the design and conduct of the submitted clinical trials and because the results as provided do not demonstrate that Decapeptyl is a safe and effective drug for the treatment of advanced prostate cancer. The deficiencies in these areas may be summarized as follows:

Study Design Deficiencies

1. Absence of a central laboratory in each of the submitted studies

   As stated in your correspondence dated March 14, 1997, none of the three studies conducted utilized a central laboratory for the measurement of testosterone. The existence of a central laboratory in studies in which the primary efficacy endpoint is laboratory-based (such as testosterone levels) is important because of variation between laboratories and within some laboratories.

2. Inadequate assessment of testosterone levels

   In each of the three studies conducted, testosterone was measured monthly for the first 3 months and every 3 months thereafter. This schedule of testosterone measurement is insufficient. To obtain useful data, testosterone levels must be monitored frequently during the first month and before and after each monthly readministration.

3. Dosing schedule inconsistent with proposed regimen

Your study reports note that Decapeptyl was administered according to different schedules during the first study month to some or to all patients. The ability of an agent in this class to induce castrate levels of testosterone at one month is an essential parameter in establishing its efficacy. Because the monthly depot was not consistently used in these studies, conclusions regarding the safety and efficacy of Decapeptyl Depot cannot be inferred.

Study Conduct Deficiencies

1. Lack of randomization to treatment groups

Two of the study reports (Protocols 914CL14P and 914CL17E) state that randomization codes were unavailable and that the studies "cannot strictly speaking, be called randomized." Further, although not stated in the study report, a clinical audit of the third study (Protocol 914CL7P) concluded that the randomization was presumed inadequate due to inadequate documentation. This lack of randomization invalidates any statistical inference.

2. Excessive loss to follow-up

Loss-to-follow-up (for reasons other than death) was unacceptably high. The highest rates of loss-to-follow-up occurred in Protocol 914CL17E (58% by 12 months and 88% by 24 months) and Protocol 914CL7P (30% by 12 months and 73% by 24 months). Although the loss-to-follow-up rates were comparable between treatment groups, it is difficult to make claims of long-term safety and efficacy in the presence of substantial loss-to-follow-up.

3. Failure to achieve castrate testosterone levels in the active control (orchiectomy) group

In the three studies combined, approximately 25% of the orchiectomized patients did not achieve testosterone levels in the castrate range. This unexpected finding may be explained by clinical design problems, including:

a. A lack of a central laboratory and assay standardization; and/or

b. In some instances, patients may not have undergone complete surgical removal of the testes (orchiectomy). A literature report of Protocol 914CL17E describes an alternate operation, a "testicular pulpectomy," a procedure in which the tunica of the testicle is opened and the contents shelled out. In this procedure, there is a potential for leaving residual testes tissue. Operative reports to confirm or refute this concern and possible explanation of the unacceptably high testosterone levels in the surgically treated groups were not submitted.

4. Clinical Audit Violations

Significant deficiencies were discovered at all of the four inspected sites. These deficiencies included:

a. insufficient or non-existent documentation of randomization procedures;

b. inadequate study records with up to 42% of patient records missing;

c. inadequate documentation of patient consent in the majority of patients; and

d. protocol violations in determining patient eligibility.

Study Result Deficiencies

Notwithstanding the previously noted clinical trial deficiencies, the results do not provide a sufficient basis upon which to conclude that Decapeptyl is comparable in efficacy to surgical castration. As discussed at the pre-NDA meeting on January 18, 1995, the primary evidence of efficacy was to be based on the demonstration that Decapeptyl and orchiectomy produce comparable levels of testosterone suppression.

The cross-sectional analyses for the three studies demonstrated that more than 10% of all Decapeptyl-treated patients failed to achieve castrate testosterone levels at three-fourths of all time points measured over the two-year treatment period. Further, more than 20% of all Decapeptyl-treated patients failed to achieve castrate testosterone levels at 43% of all time points measured. Although the percentages of failures appear similar between treatment groups, the overall high percentage of patients who failed to achieve castration levels at any given time point is unacceptable.

As an alternative approach, we performed a "responder analysis" in which a clinically meaningful response was defined as reduction in testosterone to castrate levels within one month with maintenance of castrate levels throughout the course of therapy. This responder analysis yielded the results in the following table:

FDA responder analysis of the percentages of patients who achieved castrate testosterone levels at one month and at each time point thereafter, by treatment group and clinical study

	Response Rate (% success)	
Protocol Number	**Decapeptyl**	**Orchiectomy**
914CL14P	20/72 (27.8%)	8/44 (18.2%)
914CL17E	19/40 (47.5%)	29/39 (74.4%)
914CL7P	22/42 (52.4%)	10/15 (66.7%)

As shown, an unacceptably low percentage of Decapeptyl-treated patients had a sustained reduction in testosterone levels. Therefore, neither the results of the submitted cross-sectional analyses nor the FDA responder analysis support the efficacy of Decapeptyl.

Statistical

The data sets submitted did not contain an identifier, as requested, for the various laboratories used for the studies performed. Therefore, the variation in testosterone levels due to the use of several laboratories could not be assessed.

Biopharmaceutics

1. Based on the Agency's 90% confidence interval criteria, the provided data from the bioequivalence study (AUC and C_{max} of triptorelin) indicate that the proposed to-be-marketed formulation and the formulations used in the clinical studies are not bioequivalent.

2. The provided pharmacodynamic bioequivalence information comparing the pharmacodynamics (maintenance and suppression of serum testosterone levels) of the to-be-marketed formulation and that of the clinically tested formulations under single-dose conditions is not acceptable. The proposed to-be-marketed formulation exhibits a "spike" in the triptorelin concentration within 3 hours of administration. This spike may result in secondary flares of testosterone on readministration during chronic use, resulting in escapes from castrate levels. Therefore, additional data under multiple-dose conditions are needed to support the pharmacodynamic bioequivalence of Decapeptyl.

Manufacturing/Quality Control

1. The proposed expiration date, [redacted] for pre-filled syringes is not acceptable. A comparable expiration date to the drug vial should be established with supporting stability data. [redacted] the expiration date of the pre-filled syringes should be set from the date that the Water for Injection is filled into the syringe.

2. The amount of the major degradation product [redacted] from the three full-scale production batches exceeded the release specification ([redacted]%) after [redacted] months at [redacted] Therefore the proposed [redacted] expiration date for the depot is not acceptable. Either the expiry date or the storage condition should be changed.

Microbiology

1. [redacted] Sterilization of the Debiojects

   a. The name and address of the [redacted] sterilization facility should be submitted.

   b. Data on the measurement of [redacted] in the diluent after [redacted] sterilization must be provided. In addition, reports on the levels and acceptance criteria should also be submitted.

2. Media Fill Studies to Validate the Aseptic Connection of Debioject Delivery System to Decapeptyl Vials

   Data for media fills should be submitted.

3. Container-closure integrity

   a. Data for container-closure integrity should be submitted.

   b. The duration of microbial immersion of the vials and the incubation period after the challenge appear short. These times should be increased to at least 2 hours.

   c. The sensitivity of the dye ingress should be provided (the minimum volume of the dye for detection).

   d. To assess the integrity of the rubber stopper on the top of the pre-filled syringe, the entire Debioject system should be immersed inside the dye solution.

We also have the following comments and requests for information that should be addressed:

Biopharmaceutics

The proposed dissolution testing method is not acceptable. The proposed paddle speed (200 rpm) may result in shearing or breaking of the microgranules rather than dissolution. The *in vitro* dissolution methodology described below has been used in the quality control of a currently approved product with a similar formulation to that proposed for Decapeptyl™.

Apparatus: USP Type II glass (120 mL)
Medium: 0.4% polyvinyl alcohol, 0.1% polysorbate 80, and 20 mM lactic acid
Procedure:

We recommend that you use a similar methodology to the above with paddle speeds of [redacted] rpm. Complete individual and mean dissolution profiles (numerical and graphical) from at least 12 units of the clinical lot(s) and from a full-scale batch of the proposed to-be-marketed product should be submitted for review. Samples should be collected every 1-4 hours until complete dissolution is achieved or a plateau is reached. Dissolution specifications for a minimum of three points (four are preferable) should be proposed; the last point should be set at [redacted]% of drug dissolved. The proposed ranges should be based on mean ± 10% of the bio/clinical lot(s) dissolution data.

Manufacturing/Quality Control

1. The amino acid analyses (Vol 1.2, p 76) of the three batches (23288, 22171, 21379) indicate [redacted] were detected as [redacted]. Please clarify.

2. You indicate (Vol 1.2, p 78) that according to [redacted] spectrum, the mass data are consistent with the proposed structure. However, only two [redacted] of nine m/z peaks were identifiable in the submitted spectrum. Other mass spectral data (Vol 1.2, pp. 88-89) showed a major peak at [redacted] and other m/z peaks; however, [redacted] m/z cannot be identified (lot 502527) in the spectra, although they were stated to be observed. This discrepancy should be clarified.

3. [redacted] co-elution data (Vol 1.2, p 85) were submitted to demonstrate that the peptide in triptorelin acetate and triptorelin pamoate are the same. You indicate that the retention time of the peptide is [redacted] minutes; however, the chromatograms indicate its retention time is approximately [redacted] minutes. This discrepancy should be clarified.

4. The amount of triptorelin pamoate and poly(d,l-lactide-co-glycolide) in the batch formula for 1200 vials (Vol 1.2, p 126) are not corresponding to those of the composition of one vial. Please provide an explanation.

5. The composition data of investigational formulations used in clinical studies should be provided.

6. [redacted] At least one identification test must be performed on all batches.

7. The date of manufacture for triptorelin microgranules is defined as the date that [redacted] sterilization is completed. Because stability of the drug product is based on [redacted] of the peptide, this is not acceptable. The date of manufacture should be the date that the vials are lyophilized and sealed, and the expiration date should be set from this date.

8. You indicate (Vol 1.2, p 258) that pre-filled syringes were labeled as "Sterile diluent" rather than "Sterile Water for Injection." Because specifications for pH, chloride, and residue on evaporation could exceed the USP specifications, it should be labeled as "Sterile Water for Injection, USP" with justified new specifications for pH, chloride, and residue on evaporation on the label.

9 The expiration date for each drug vial and pre-filled syringe should be imprinted individually and the shortest-dated component should be imprinted on the blister package as well as on the carton.

10. Additional deficiencies have been sent, under separate cover, to the Drug Master File (DMF [redacted] holder.

Microbiology

1. [redacted] sterilization of Decapeptyl vials

   The determination of spore survival in [redacted] -sterilized vials measures the effect of [redacted] as well as any possible inhibitory effect of Decapeptyl. Information on the effect of this drug product on spore germination should be provided. In addition, data should be submitted to demonstrate the effect of Decapeptyl on spore counts.

2. Stability programs of the drug product

   There appears to be a high risk of contamination due to the configuration of the drug product and its associated components. Container/closure integrity of the entire Decapeptyl Debioject system should be performed with the stability samples at release as well as at expiry.

We will provide comments on your proposed labeling when other aspects of your application are found satisfactory. Also, we remind you that satisfactory inspections of the manufacturing facilities must be completed before the application may be approved.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendments should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal or telephone conference with the Division to discuss what further steps need to be taken before the application may be approved.

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

Sincerely,

/S/

James Bilstad, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

NDA 20-715
Trelstar® Depot (triptorelin pamoate for injectable suspension)
Debio Recherche Pharmaceutique S.A.

There are no Phase 4 Committments.

274 pages redacted from this section of the approval package consisted of draft labeling