# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPROVAL PACKAGE FOR:

## APPLICATION NUMBER
## 21-288

# Administrative Documents

EXCLUSIVITY SUMMARY for NDA # 21-288 SUPPL # _____
Trade Name Trelstar™ LA 11.25 mg
Generic Name triprorelin pamoate for injectable suspension
Applicant Name Debio Recherche Pharmaceutique S.A. (c/o Target Research Associates HFD- 580
Approval Date June 29, 2001

**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 questions 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?

YES /___/ NO /X_/

**IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

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 # _____ Drug Name _____

**IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

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 9 (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 /X/ NO /___/

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

NDA # 20-715 Trelstar™ Depot 7.5 mg

NDA # _____ _____

NDA # _____ _____

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).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

**IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.**

**PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>**

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 /X/ NO /___/

**IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(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 /X/ 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 9:**

_____

_____

(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 /X/

(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 /X/

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:

Investigation #1, Study # DEB-96-TRI-01, first phase

Investigation #2, Study # DEB-99-TRI-01

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 /X/

Investigation #2 YES /___/ NO /X_/

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

NDA # _____ Study # _____

NDA # _____ Study # _____
NDA # _____ Study # _____

(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 /X/

Investigation #2 YES /___/ NO /X/

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

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(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"):

Investigation #1 , Study # DEB-96-TRI-01, first phase

Investigation #2 , Study # DEB-99-TRI-01

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

IND #[ ____ ] YES /X_/ ! NO /___/ Explain: _____

_____

_____

Investigation #2

IND #[ _____ ] YES /X/ ! 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 /X/

If yes, explain: _____

_____

_____

/S/

_____ _____
Signature of Preparer Date
Title:_____

/S/

_____ _____
Signature of Office or Division Director Date

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

## PEDIATRIC PAGE (Complete for all original application and all efficacy supplements)

View as Word Document

| | | | |
|---|---|---|---|
| **NDA Number:** | 021288 | **Trade Name:** | TRELSTAR LA(TRIPTORELIN PAMOATE FOR INJ |
| **Supplement Number:** | 000 | **Generic Name:** | TRIPTORELIN PAMOATE FOR INJECTABLE SUSP |
| **Supplement Type:** | N | **Dosage Form:** | |
| **Regulatory Action:** | OP | **COMIS Indication:** | PALLIATIVE TREATMENT FOR ADVANCED PROSTATE CANCER |
| **Action Date:** | 6/29/01 | | |

**Indication # 1** Palliative treatment of advanced prostate cancer

Label Adequacy: Does Not Apply

Formulation Needed: NO NEW FORMULATION is needed

Comments (if any):

**Ranges for This Indication**

| Lower Range | Upper Range | Status | Date |
|---|---|---|---|
| Adult | Adult | Waived | |

Comments: prostate cancer is an adult male disease

**This page was last edited on 6/28/01**

Signature

6/29/01

Date

...LTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

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

# CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

*TO BE COMPLETED BY APPLICANT*

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

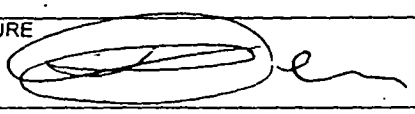
*Please mark the applicable checkbox.*

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

| Clinical Investigators | | |
|---|---|---|
| | ~~list attached~~ | |
| | | |
| | | |

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

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

| NAME | TITLE |
|---|---|
| Orsolini Piero | CEO |
| FIRM/ORGANIZATION: Debio Recherche Pharmaceutique S.A. | |
| SIGNATURE:  | DATE: April 20th, 2000 |

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

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Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

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## Deputy Division Director's Memorandum

**NDA** 21-288

**Applicant** Debio Recherche Pharmaceutique SA
Case Postale
Route du Levant 146
CH – 1920 Martigny
Switzerland

**Submission Type** Original NDA

**Drug**

**Established name** Triptorelin pamoate for injectable suspension

**Trade name** Trelstar LA

**Chemical class** Synthetic decapeptide

**Chemical name** Pyr-His-Trp-Ser-Tyr-D-Trp-Leu-Arg-Pro-Gly-NH2 pamoate salt
(D-Trp$^{6}$-GnRH)

**Drug Class** Gonadotropin releasing hormone (GnRH) agonist

**Proposed Indication** Palliative treatment for advanced prostate cancer.

**Route of Administration** Intramuscular injection

**Dosage Form** Suspension

**Dosing Regimen** Administered once every 84 days (every 12 weeks)

**Dose** 11.25 mg per dosing

**Dates**

**Submitted** June 29, 2000

**CDER stamp date** June 29, 2000

**PDUFA date** June 29, 2001

**Related NDAs** 20-715

**Related INDs** IND[ ]
IND[ ]

**Review Completed**: June 29, 2001

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Conclusionary Remarks:

I agree with the primary medical officer and urology team leader that Trelstar LA should be approved with the phase 4 commitment described in the Tcon between the sponsor and the division on June 21, 2001 and the letter from the sponsor to the Agency on June 22, 2001.

On June 29, 2001 the Division and the sponsor agreed upon all outstanding labeling issues.

/S/ 6/29/01

Daniel A. Shames MD
Deputy Division Director
FDA/CDER/DRUDP

NDA 21-288

**Date submitted**: June 29, 2000
**Date received**: June 29, 2000
**Memo completed**: June 23, 2001

**Supervisory Medical Officer's Memorandum – Original NDA**

| | |
|---|---|
| **TO:** | Dan Shames, MD, Deputy Division Director, HFD-580 |
| **FROM:** | Mark Hirsch, M.D., Urology Team Leader, HFD-580 7/10/01 |
| **REGARDING:** | Recommendation re: NDA 21-228 |
| **Sponsor:** | Debio Recherche Pharmaceutique SA |
| **Drug:** | Trelstar LA (triptorelin pamoate for injectable suspension) |
| **Drug class:** | gonadotropin releasing hormone (GnRH) agonist |
| **Route of administration:** | intramuscular injection |
| **Dose:** | 11.25 mg |
| **Dosing regimen:** | once every 84 days (12 weeks) |
| **Proposed indication:** | palliative treatment for advanced prostate cancer |

**Executive summary:**
The purpose of this memo is to provide the Deputy Division Director with the medical team leader's recommendation for regulatory action concerning the new drug application # 21-288. This reviewer recommends *approval* of this NDA. The sponsor has submitted adequate information to support the safe and effective use of Trelstar LA as purported in the proposed label. In addition, the sponsor has committed to conduct a small Phase 4 study to provide additional information relevant to the acute-on-chronic phenomenon, and also has agreed to all recommended clinical labeling changes. Thus, from a clinical perspective, the application should be approved.

**Scientific background:**
Approximately 200,000 new cases of prostate cancer will be diagnosed in the United States this year. In a significant percentage of cases, patients will be diagnosed with locally-advanced or metastatic disease. In addition, there will be a substantial number of patients in whom curative therapy fails and recurrent or metastatic disease is noted. Androgen deprivation therapy is a well-recognized treatment for many of these patients. Palliation of painful bone metastases is a clear benefit. In locally-advanced disease, neoadjuvant androgen ablation has been associated with a delay in time to metastases. Less clear is the effect on overall prolongation of life.

Currently, there are several commercially available products for the purpose of ablating androgen in men with prostate carcinoma. These include TAP Pharmaceutical's Lupron Depot (leuprolide), Zeneca Pharmaceutical's Zoladex (goserelin), and Debio's Trelstar (triptorelin). These products result in the reduction of serum testosterone to castrate levels by initially stimulating GnRH receptors on the pituitary, which are ultimately down-regulated. These GnRH agonists are available in several different depot formulations with 1-month, 3-month and 4-month activities. They are recognized as safe and effective treatments for advanced prostate cancer.

At this time, Debio Recherche submits an application for marketing approval for an 84-day (11.25 mg) formulation of triptorelin pamoate, Trelstar LA. This follows closely the approval by this Division of its 28-day (3.75 mg) formulation, Trelstar Depot, in June 2000. The obvious benefit of such a formulation over the 28-day formulation would be patient and practitioner convenience, and ultimately better quality-of-life.

**Regulatory background:**
For detailed description of the regulatory milestones relevant to this application, please see the medical officer's excellent review Section 3.3.2. For purposes of this supervisory review, it is important to understand that the bulk of data supporting efficacy and safety for this application comes from one large, multi-center, active-controlled, trial, DEB 96-TRI-01.

DEB-96-TRI-01 was ongoing prior to the approval of the 28-day (3.75 mg) formulation of triptorelin. The sponsor had submitted a previous NDA for the 28-day formulation that received a not approvable action from the Division. In its recommendations to Debio following the NA action, DRUDP noted that DEB-TRI-01 could support approval of an 84-day formulation, if the 28-day formulation was actually approved.

In order to receive marketing approval for the 28-day formulation, the sponsor would need to conduct an additional trial comparing that formulation to an approved GnRH agonist such as Lupron. Based on this recommendation, the sponsor revised DEB-96-TRI-01 so that a second phase was added. The second phase allowed all currently enrolled patients to be re-randomized to either the 28-day formulation of triptorelin or to Lupron, 7.5 mg monthly. Phase 2 of this trial thus served to support the approval of the 28-day formulation (approved in June, 2000) and Phase 1 supports this application.

Other than phase 1 of DEB-96-TRI-01, the NDA contains additional controlled data from studies investigating the pharmacokinetics of this formulation.

Triptorelin 3.75 mg is marketed in over 60 countries, in most, under the tradename, Decapeptyl. Approximately [ ] of triptorelin have been sold in the immediate-release or depot formulations over the 10-year period from 1987-1998. The current object of this review, the 11.25 mg or 84-day formulation, is already approved in France, Belgium, Ireland, Italy, Lebanon, Portugal, and Spain. A microgranule (not microparticle) 84-day formulation has also been approved in Argentina, Mexico and Canada.

**Support for safety and efficacy from DEB-96-TRI-01**
*Design*
Phase 1 of DEB-96-TRI-01 was a randomized, active-comparator, parallel-arm design controlled clinical trial comparing the 28-day and 84-day formulations of triptorelin pamoate. Patients in the 84-day arm received 3 dosages of drug over a treatment period of 252 days, while patients in the 28-day arm received 9 dosages over the same period of time.

As discussed previously, the primary efficacy assessment was based on the patient's serum testosterone concentration during treatment. The primary objective was to demonstrate that the 84-day formulation of triptorelin was not inferior to the 28-day formulation as assessed by:

1. The proportion of patients achieving castrate levels of serum T (≤ 1.735 nmol/L) on Study Day 29, and
2. The proportion of patients maintaining castrate levels from Month 2 (Study Day 57) through Month 9 (Study Day 253).

For endpoint #1 (proportion achieving castration), a non-inferiority limit of −10% was applied to the lower bound of the 95% confidence interval for the difference between the proportions in

each arm. Therefore, by prior agreement, if the lower bound of the confidence interval was not lower than –10%, then non-inferiority for this endpoint could be claimed.

For endpoint #2 (proportion maintaining castration), non-inferiority was assessed using two procedures. In the first, the probability of a patient maintaining castration levels from Month 2 to Month 9 was estimated using survival analysis techniques (Kaplan-Meier method). In the second, the observed monthly maintenance of castration within the time interval of Month 2 to Month 9 was derived for each patient and each treatment group. As an additional analysis, the percentage of patients in each treatment group with castrate T levels at each visit was also presented.

It should be noted that a subset of 30 patients at Study Center #1 underwent more frequent blood sampling, for the purpose of investigating the potential for an acute increase in serum T (above castrate level) following repeated dosing.

*Results*

Three hundred forty-eight (348) patients were randomized at 19 centers in South Africa (174 into the 84-day arm and 172 into the 28-day arm). There were 335 patients included in the intent-to-treat population (171 and 164 in the 84- and 28-day arms, respectively). These losses are clearly accounted for and are considered reasonable. Ultimately, only 10 patients were excluded fom the per-protocol population and again, these exclusions were accounted for and were acceptable. The two arms were well-matched demographically.

In the ITT population, 167 out of 171 patients (97.7%) in the 84-day arm achieved castration by day 29, compared with 152 out of 164 patients (92.7%) in the 28-day arm. The difference was 5.0% with CI of (-1.1%, 13.4%). Thus, based on prior agreement where the lower bound of the 95% CI could be no lower than –10%, non-inferiority was demonstrated.

In the ITT population, using the Kaplan-Meier method, the cumulative maintenance of castartion from Day 57 through Day 253 was 94.4% for the 84-day formulation and 94.2% for the 28-day formulation. The difference was thus 0.2%, with 95% CI of (-4.9%, 5.3%). Using the average monthly maintenance method and the ITT, the average monthly maintenance in the 84-day group was 96.5% compared to 95.2% in the 28-day group. Again, based on prior agreement and by demonstration of very clear results, non-inferiority was demonstrated.

In regard to the assessment of safety, it is clear that the majority of exposure is limited to DEB-96-TRI-01, where approximately 165 and 156 patients received 2 and 3 doses of the 84-day formulation, respectively. Although this is a relatively small database, there are mitigating factors, as follows:

1. there is a substantial safety database for the 28-day formulation
2. there is a long previous human experience with triptorelin
3. there is a vast amount of experience with the GnRH agonists as a drug class

Given these caveats, the safety results demonstrated no new concerns for this new 84-day formulation. The majority of adverse reactions reported in both groups were related to either the pharmacologic action of the drug (e.g. hot flushes) or to concomitant morbidity associated with prostate cancer (e.g. skeletal pain) or aging.

Of note, GnRH agonists are known to initially stimulate the release of serum T, sometimes associated with clinical symptoms (a flare). In the majority of these instances, the flare is limited

to symptoms of bony pain, however, other more serious consequences have been reported (e.g. paralysis). In this program, two patients in the 84-day group reported adverse events possibly related to a "flare". One patient reported increased skeletal pain and one patient (No. 1017) reported transient weakness of the legs considered related to a clinical flare by the investigator. These reports do not stand out as unique or more severe in this group of patients than any group previously treated with GnRH agonists. In addition, the label does advise cautious use of GnRH agonists in men at high risk for flare.

Again of note, triptorelin is a peptide and has been noted to be associated with rare reports of hypersensitivity or "allergic-type" reaction. In this safety database, no severe systemic allergic reactions were reported. However, as described by the medical officer in his Table 35, there have been a few post-marketing reports of severe allergic reaction over the course of several years, including 3 cases of anaphylaxis from the Years 1997 through 2000. Again, the label is clear in describing the rare potential for such an event.

**The acute-on-chronic phenomenon**
As previously stated, GnRH agonists initially stimulate the secretion of LH and serum T prior to ultimately driving down the serum concentrations of these hormones. Since the agents ar given on a periodic basis and in depot form, it is important to assess whether a re-injection induces a "spike" of serum T, above the castrate level. This sort of investigation is a usual consideration in the development of novel formulations of the GnRH agonists.

In this case, the sponsor did conduct investigations into this matter. However, the bulk of their assessments centered on repeated measures of serum LH. The sponsor intended to show that repeated dosing of Trelstar LA did not lead to an increased percentage of patients demonstrating an increase in serum LH of > 1 IU/L compared with Trelstar Depot. In both groups, more than 90% of patients had an increase in serum LH that was actually less than 1 IU/L.

The sponsor believed that serum LH measurements could be used to assess this "acute-on-chronic" phenomenon. Nevertheless, they did perform some of this type of investigation using serum T as an endpoint. Appropriate testosterone data was available from 15 patients after the Day 85 dose and 14 patients after the Day 169 dose. No patient in either arm demonstrated an increase in serum T over castrate level at Day 85. Two patients in the 84-day arm demonstrated an increase in serum T over castrate level at Day 169. In one patient the maximum serum T was 1.79 n/mol/L (castrate level = 1.735). In the other patient, the maximum serum T was 2.65 nmol/L. Neither of these patients demonstrated an increase in serum LH.

Based upon these results, which do not appear to suggest a signal of the acute rise upon chronic supression phenomenon, there does not appear to be a safety concern. However, in order to obtain more information in this regard, the sponsor was asked to conduct a small "acute-on-chronic" study and they agreed to do so.

**Clinically relevant information from other disciplines**
*Clinical pharmacology:*
There are no outstanding issues noted in the Clinical Pharmacology review.

*Toxicology:*
There are no outstanding issues noted in the Toxicology review.

*Biometrics:*
The statistician's review confirms the conclusions by the medical officer.

*Microbiology:*
According to the microbiology reviewer's memo, all microbiology deficiencies from the first microbiologist's review were resolved either by the sponsor's amendment or via a February 15th teleconference between the microbiology reviewer and the sponsor.

*Chemistry*
There remain two outstanding chemistry issues that relate to labeling. In the first, the sponsor has agreed to revise the carton labeling so that the frequency of dosing is clearly displayed and the symbol for micrograms is changed to the actual word "micrograms"(as per OPDRA's recommendation), but the revised carton has yet to be received by the Division. Apparently, the sponsor has stated that it is "at the printers". In the other, it appears as though the "same storage statement that is printed on the vial label needs to be added to the pre-filled syringe label". I am unsure where that issues stands currently.



APPEARS THIS WAY
ON ORIGINAL

**MEMORANDUM**

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

**DATE:** June 29, 2001

**TO:** NDA 21-288 (original submission)

**FROM:** Scott Monroe, MD
Medical Officer, HFD 580

**SUBJECT:** OPDRA Review of Labeling for Trelstar™ LA

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The labeling changes recommended by OPDRA were reviewed by the Clinical Team reviewing NDA 21-288 and the following recommendations are made.

1. **OPDRA recommendation concerning labeling of container, cartons and package.**
We concur that the dosing interval should be included as part of the labels for the container, carton, and package. We recommend, however, that the terminology "once every 3 months" not be used in any labeling. Only the terms "84 days" or "12 weeks" should be used in all references to the dosing frequency or duration of drug action. The clinical trials were conducted with a dosing interval of 84 days or 12 weeks and not 3 months (which is actually 13 weeks). The package label (as described on pg. 4 and 5 of the OPDRA consult) should read as follows:

**Trelstar LA: "GIVE ONCE EVERY 84 DAYS (12 WEEKS)"**

2. **OPDRA recommendation to include final concentration of the product in mg-per-mL after reconstitution.**
We believe that it would not be helpful (and perhaps harmful) to express the dosage of reconstituted Trelstar as mg per mL as this might suggest that dose reduction is permissible for the indication of prostate cancer. Administering less than the total dose of 11.25 mg is likely to result in inadequate suppression of testosterone and significantly reduced efficacy. Therefore, we recommend against making this addition to the label.

cc:
Archival NDA 21-288
HFD-580/Div. Files
HFD-580/S. Allen, D Shames, M. Hirsch, J. Best

## MEMORANDUM OF TELECON

DATE: May 25, 2001

APPLICATION NUMBER: NDA 21-288

BETWEEN:

Name: Robert J. McCormack, Ph.D., Vice President Regulatory Affairs
Phone: (908) 464-7500
Representing: Target Research Associates

AND

Name: Jeanine Best, R.N., M.S.N., Regulatory Project Manager
Division of Reproductive and Urologic Drug Products (HFD-580)

SUBJECT: Medical Officer Information Request

Please provide the following information to facilitate the review of NDA 21-288:

1. Please provide an update on the worldwide market authorizations or regulatory status for the 3-month formulation of triptorelin. In the update, please follow the format that was used on pg. 001 of Volume 1.39 in your original submission of June, 29, 2000 with the following modifications:
   a) Add the product launch date for each approval.
   b) Also include in the listing all countries in which a regulatory action regarding product approval is pending or for which an application for approval was withdrawn. If withdrawn, please provide the reason for the withdrawal.

2. Please clarify in what countries, if any, the microgranule formulation (in contrast to the microparticle formulation) is presently marketed and the launch date for each of the respective countries.

3. Please provide a listing of all regulatory actions since 1996 for the 3-month formulation (both microparticle and microgranule formulations) related to safety or efficacy issues, including but not limited to labeling changes regarding safety or efficacy, letters to physicians, product withdrawals.

4. Please provide the Annual Periodic Safety Update Report from the Beaufour-Ipsen Group for the period following that represented in your Safety Update of October 24, 2000. Presumably, this update will cover the period from March 5, 2000 to March 5, 2001.

5. Please provide additional information concerning the allergic reactions referred to in Table 4 (Incidence of Triptorelin Hypersensitivity Reactions...) on page 53 of the Safety Update of October 24, 2000. In particular, please provide specific information for 40 allergic events represented in the Table, using the format of Appendix IV of the Safety Update (see pg. 95 for format).

6. Please provide a listing of all cases of serious or severe allergic reactions (other than those confined to the injection sites) that have been reported with the use of any formulation of triptorelin. The proposed label states that "three post marketing cases of anaphylactic shock and seven postmarketing reports of angioedema related to triptorelin administration have been reported since 1986." This incidence appears to be incorrect (too low) based on the very limited data presented in Table 4 of the Annual Periodic Safety Update Report from the Beaufour-Ipsen Group (see Item 5 above) and the cases of

allergic reaction contained within that report for the period from March 5, 1999 to March 5, 2000. Please follow the format of the listing in Appendix IV of the Safety Update and cover the period from 1986 (since this referred to in the proposed label) through the present. Please include in the description of each adverse event the verbatim and preferred terms, outcome, seriousness, causality, relation of the event to the time of dosing (e.g., time after dosing in minutes, hours, days, etc.), and any medical intervention that was required.

7. Please provide a copy of the currently approved label in Ireland and English translations of the currently approved label in France for both the 1 and 3 month formulations of triptorelin and the EU label, if EU approval has been obtained or is being sought.

8. Please clarify the period to which the sales figures in Table 1, pg. 27 of the October 24, 2000 Safety Update refer. In particular, what is the time frame for the final sentence on pg. 27 referring to [ ]treatment months of sales? Can you also estimate the worldwide number of treatment months of sales for the 1-month and 3 month formulations since their respective launches?

5/25/01

/S/

*{See appended electronic signature page}*

Jeanine Best, R.N., M.S.N.

# MEMORANDUM OF TELECON

DATE: May 30, 2001

APPLICATION NUMBER: NDA 21-288

BETWEEN:

Name: Christian George and Pierre Orfloni
Phone: (908) 464-7500
Representing: Debio Recherche Pharmaceutique S.A. (Target Research Associates)

AND

Name: David Lin, Ph.D and Jeanine Best, M.S.N., R.N.
Division of Reproductive and Urologic Drug Products

SUBJECT: Chemistry Stability Specifications

- the clinical trial batches are used to set the specifications
- submit an amendment with an agreement to set the stability specifications the same as the release specifications; the mean $\pm$ 10 %
- further discussion can occur post-approval after more data is are generated (this includes testing more than six (6) samples at each stability time point; following the acceptance criteria for Drug Release <724> in USP 24)

/S/

Jeanine Best, M.S.N., R.N.
Regulatory Project Manager

cc:
Archival NDA 21-288
HFD-580/Division Files
HFD-580/DLin

Drafted by: JAB/May 30, 2001
Initialed by: Dlin05.30.01
Final: JAB/May 30, 2001

**TELECON**

# RECORD OF TELEPHONE CONVERSATION IN CONSULT TO HFD-580

February 15, 2001

| | |
|---|---|
| **NDA:** | 21-288 |
| **DRUG PRODUCT:** | Trelstar LA 11.25 mg |
| **CALL INITIATED BY:** | David Hussong, Ph.D., HFD-805 |
| **FIRM:** | Target Research Regulatory Affairs & Biostatistics |
| **CALL PLACED TO:** | Robert J. McCormack, Ph.D.<br>VP, Regulatory Affairs |
| **PHONE NUMBER:** | (617) 503-8000 |

Dr. McCormack sent a communication (February 2, 2001) to the NDA file in response to deficiencies from Microbiologist's Review #1. The deficiencies asked for container integrity test data for the new packaging, validation of the sterility test (bacteriostasis and fungistasis) and methods of selecting samples for the release tests (sterility and endotoxins).

In his communication, Dr. McCormack requested guidance concerning the scope of the response to the question concerning package integrity and indicated his intent to file data from physical tests. In our telephone conversation, I advised Dr. McCormack of the need for tests that demonstrate the barrier to microbiological contamination. These test should challenge the outer packaging (blister pack with cover) and the Debioclip dosage form. The tests of the Debioclip should demonstrate that it would remain sterile in the clinical setting after removal from the blister package, and I indicated the area of concern was the interface of the needle and stopper.

I added that, with a new package such as this, a study is commonly done to show the ruggedness of the packaging to withstand the stresses of shipping. These tests might employ simulated conditions, such as exposure to pressure changes (to simulate air shipment), shaking and bouncing. Dr. McCormack asked about microbiological methods to assess the integrity of the packages, and I referred him to the Technical Report 27 of the Parenteral Drug Association.

Due to the timing of this amendment and the applicant's need for test data, I requested that tests of the blister package and the tests of the interface of stopper and needle, be filed as soon as possible. Since the shipping challenge study requires additional time, I offered to accept these as a Phase 4 commitment to the NDA. Dr. McCormack agreed to provide these data and to commit to the shipping studies.

/S/ 2/20/01

David Hussong, Ph.D., HFD-805

CC: Original NDA 21-288
HFD-580/Division File
HFD-580/J. Best
HFD-160/Consult File
HFD-805/D. Hussong

# MEMORANDUM OF TELECON

DATE: January 8, 2001

APPLICATION NUMBER: NDA 21-288

BETWEEN:

Name: Dr. Mary Lou Zett
Phone: (908) 464-7500
Representing: Target Research Associates for Debio Recherche Pharmaceutique S.A.

AND

Name: Jeanine Best, MSN, RN
Division of Reproductive and Urologic Drug Products, HFD-580

SUBJECT: Clinical Information Request

1. Please document all protocol deviations involving dosing; specifically all listed in Data Listing 16.2.2 that affected classification or censoring of a patient.

2. Please resolve apparent inconsistencies between data listing 16.2.2 regarding dosing violations and the electronic dosing file and the paper dosing listing (Data Listing, 16.2.5.2). In particular, dosing (cross over violations) for patients 2006, 15025, and 9015 are referred to in listing 16.2.2, but do not appear in listing 16.2.5.2.

3. Please expand Electronic File (Injection of Study Medication) to include the injection data (calendar date), the actual study day, and the difference between the actual day and the target day (see attached for example).

Jeanine Best, MSN, RN,
Regulatory Project Manager

# MEMORANDUM OF TELECON

DATE: December 21, 2000

APPLICATION NUMBER: NDA 21-288

BETWEEN:

Name: Jill Powers
Phone: (908) 464-7500
Representing: Target Research Associates

AND

Name: Jeanine Best, R.N., M.S.N., Regulatory Project Manager
Division of Reproductive and Urologic Drug Products (HFD-580)

SUBJECT: Medical Officer Information Request

Please provide the following additional information and electronic file modifications:

1. Please add the following to electronic file
   a) A column that includes the actual calendar date of the blood sample or visit.
   b) A column that includes the actual Study Day with day of first dosing as Day 1. Presently the Table includes only the "Target Date" of the visit.
   c) Modify the column listings for Testosterone, LH, and FSH so that values below the sensitivity of the assay are identified as BLQ (or similar designation). Visits for which there are no values can be left blank. The electronic listing does not presently differentiate between values that are BLQ and those that are not available.
2. The information submitted in support of "assay quality control" in not entirely clear. In particular, it is not possible to interpret the information contained in the Murex Quality Assessments. For example, is a score of "10" better or worse than a score of "2." (see pgs 99-102 of Vol. 1.33). It also is not clear how the laboratory can ensure that values for testosterone are stable throughout the study period if the target ranges for the testosterone assay controls change every few months (presumably due to changes in QC lots). Please resolve these issues.
3. For paper and electronic listings of unique adverse events (paper listing 16.2.8.2 and electronic file AE.xpt), please modify to include the following additional information:
   a) Onset date for each adverse event also expressed as Study Day with day of first dosing as Day 1.
   b) Duration of each adverse event.
   c) For each subject, sort (list) AEs by onset date.

4. For electronic listing of safety lab data (file please reformat table so that visits are represented as columns and not rows. The desired general format is shown below:

| Pt ID | Lab Test | Pre Treat | NI ? | Day 1 | NI? | Day 85 | NI? | Day 169 | NI? | Day 253 | NI? |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | |

List by treatment group, patient ID, and lab test. Are values outside of the normal range "flagged" in the file ?" If values are flagged, were normal ranges for each lab used as safety data were apparently measured locally?

5. Please have the laboratory that performed the testosterone assays provide the Division with a listing (prepared by the lab directly from source documents) of all final testosterone values submitted in support of the NDA. The listing should include

   a) Subject number

   b) Date of sample (and time if multiple samples obtained on a single day)

   c) Final testosterone value

   d) Both a paper and electronic copy (SAS export file or in Excel 97 or older version) should be provided

This request is being made because (1) testosterone is the endpoint for the primary efficacy assessments, (2) confirmation that the values in the Sponsor's database are identical to those provided by the lab is desirable because of the possibility of entry errors, and (3) the Sponsor did not provide specific information in the submission as to how the lab data were transmitted to the Sponsor (e.g., electronically, by paper copy, indirectly from the Investigator via the CRF, etc.

Jeanine Best, R.N., M.S.N.

**Memorandum**

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

Date:

From: David Hoberman, HFD-715

Subject: Castration rates using 3 month Trelstar

To: File: (NDA#21-288)

Dr. Monroe of the DRUDP requested that I analyze the Trelstar data in two ways in order to confirm the sponsor's results. In the first case, the data follows that of the sponsor's in which failure (lack of testosterone castration level) could occur starting from day 29 on. The second way is a modification in which failure can occur by day 57. In the first case, the Kaplan-Meier estimates for success (castration by 29 days which is maintained throughout the trial) were 89% for the 1-month formulation and 95% for the 3-month formulation. The 95% confidence interval for the difference (3-month regimen- 1-month regimen) is (0%, 12%). In the second case, the Kaplan-Meier estimates of success (castration by day 57 which is maintained throughout the trial) were 95% for the 1-month formulation and 96% for the 3-month formulation. The 95% confidence interval for the difference (3-month regimen - 1-month regimen) is (-3.8%, 5.8%).

David Hoberman, Ph.D.
Mathematical Statistician

cc:
Arch NDA# 21-288
HFD-580
HFD-580/DShames, MHirsch, SMonroe, JBest
HFD-715/DHoberman, LKammerman

**CONSULTATION RESPONSE**
**Office of Post-Marketing Drug Risk Assessment**
**(OPDRA; HFD-400)**

| **DATE RECEIVED:** August 30, 2000 | **DUE DATE:** March 1, 2001 | **OPDRA CONSULT #:** 00-0240 |
|---|---|---|

**TO:** Susan Allen, M.D.
Director, Division of Urologic Drug Products
HFD-580

**THROUGH:** Jeanine Best, M.S.N., R.N., Regulatory Project Manager
HFD-580

| | |
|---|---|
| **PRODUCT NAME:** Trelstar LA (triptorelin pamoate for injectable suspension; 11.25 mg per vial) | **MANUFACTURER:** Debio Recherche Pharmaceutique, Route du Levant 146 CH-1920 Martigny, Switzerland |
| **NDA #:** 21-288 | **DISTRIBUTOR:** Pharmacia & Upjohn Co. Kalamazoo, MI 49001 |

**SAFETY EVALUATOR:** Carol Pamer, R.Ph.

**SUMMARY:** In response to a consult from the Division of Urologic Drug Products (HFD-580), OPDRA conducted a review of the proposed proprietary name "Trelstar LA" to determine the potential for confusion with approved proprietary and generic names as well as pending names.

**OPDRA RECOMMENDATION:** From a safety perspective, OPDRA has no objections to the use of the name "Trelstar LA". We have also made recommendations for labeling revisions to minimize potential errors with the use of this product. See the checked box below.

FOR NDA/ANDA WITH ACTION DATE BEYOND 90 DAYS OF THIS REVIEW
This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDAs from the signature date of this document. A re-review request of the name should be submitted via e-mail to "OPDRAREQUEST" with the NDA number, the proprietary name, and the goal date. OPDRA will respond back via e-mail with the final recommendation.

☒ FOR NDA/ANDA WITH ACTION DATE WITHIN 90 DAYS OF THIS REVIEW
OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDAs from this date forward.

FOR PRIORITY 6 MONTH REVIEWS
OPDRA will monitor this name until approximately 30 days before the approval of the NDA. The reviewing division need not submit a second consult for name review. OPDRA will notify the reviewing division of any changes in our recommendation of the name based upon the approvals of other proprietary names/NDAs from this date forward.

/S/

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

/S/

Martin Himmel, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

JUL 17 2000

# MEMORANDUM

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

**Date:** July 17, 2000

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

**Subject:** Review of Financial Disclosure documents

**To:** The file (NDA 21-288)

I have reviewed the financial disclosure information submitted by Target Research Associates on behlaf of of Debio Recherche Pharmaceutique SA (Debio, R.P.) in support of NDA 21-288.

One large study was conducted to support the safety and efficacy for Trelstar LA (11.25 mg). The study number and its outcome with regard to financial disclosure obligations is summarized below:

| Study No. | Study Status | Financial Disclosure Documentation |
|---|---|---|
| DEB-96-TRI-01 | Ongoing as of February 2, 1999 (completed February 11, 1999) | Appropriate documentation; no financial arrangements or proprietary interest |

**Conclusion:**

Adequate documentation has been provided to ensure that the sponsor is in compliance with 21 CFR 54. The sponsor had 100% compliance in regard to obtaining the appropriate documentation from the investigators.

cc:
Orig NDA 21-288
HFD-580/JBest

Redacted 1

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confidential

commercial

information