CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-437

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum: Internal Labeling Consult

Date: **March 8, 2010**

To: **Kim Robertson, Project Manager, DDOP**

From: Keith Olin, Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

Subject: NDA # 22-437
DDMAC PI labeling comments for Trelstar (triptorelin pamoate) for injection, 3.75mg, 11.25mg, 22.5mg

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DDMAC has reviewed the proposed PI for Trelstar (triptorelin pamoate) for injection submitted for consult, and offers the following comments. Comments regarding the proposed PI were discussed at the March 3, 2010 labeling meeting with the Division of Drug Oncology. DDMAC used the draft labeling sent on 2/24/10.

(b) (4)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22437	ORIG-1	WATSON LABORATORIES INC	TRELSTAR [redacted] (b) (4)

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/s/

KEITH J OLIN
03/08/2010

Department of Health and Human Services

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology

Date:	March 2, 2010
To:	Robert Justice, MD Division of Drug Oncology Products
Through:	Kellie Taylor, Pharm D, MPH, Team Leader Carol Holquist, RPh, Director Division of Medication Error Prevention and Analysis
From:	Cathy A. Miller, BSN, MPH, Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name(s):	Trelstar (Triptorelin Pamoate) for Injectable Suspension 22.5 mg
Application Type/Number:	NDA # 022437
Sponsor:	Watson Pharmaceuticals
OSE RCM #:	2009-894

CONTENTS

EXECUTIVE SUMMARY

Triptorelin Pamoate is currently marketed in a 3.75 mg strength under the name Trelstar Depot, and a 11.25 mg strength, under the proprietary name, Trelstar LA. The Applicant's pending application NDA 022437 introduces a third 22.5 mg strength to the product line, and they have submitted a proposal to manage all three products under the single proprietary name, Trelstar. We found the proposal to manage all three products under the proposed name 'Trelstar' acceptable in our July 22, 2009 Proprietary Name Reviews (OSE #2009-893, 2009-920 and 2009-921) contingent upon the approval of NDA 022437 and continue to support the Applicant's proposal.

Both the Division of Drug Oncology Products (DDOP) and the Division of Medication Error and Prevention Analysis (DMEPA) feel that it is important to provide differentiation through product labels and labeling if all three strengths are managed under the same name, Trelstar. As such, DMEPA considered the vulnerability of managing all three products under the single name, Trelstar.

DMEPA reviewed the labels submitted by the Applicant on May 9, 2009 and draft labeling submitted by the Applicant on June 29, 2009, and finds no vulnerabilities that may introduce medication errors in the clinical setting. Additionally, we concur with the Division of Drug Oncology Product's decision to deny the Applicant's February 3, 2010 proposal to add the word [redacted] (b) (4), to the Section 2.1 Dosing Table 1 of the insert labeling. As DMEPA and DDOP discussed at an internal meeting on February 23, 2010, product labels and labeling should reflect the Trelstar study design including the endpoint measured in weeks.

DMEPA recommends that the Division attempt to coordinate regulatory action for this application with pending actions for prior approval supplement revisions for the proposed proprietary name change, along with proposed labels and labeling revisions to Trelstar Depot and Trelstar LA (NDA 020715/S-018 and 021288/S-015. This coordinated effort will help facilitate the transition of the Trelstar product line through the Applicant's Communication and Marketing Plan for the Trelstar and may minimize product confusion in the clinical setting.

1 BACKGROUND

1.1 INTRODUCTION

This review is in response to a request from the Division of Drug Oncology Products (DDOP) for the review of labels and labeling originally submitted by Watson Pharmaceuticals on May 4, 2009, for new drug application (NDA 022437).

1.2 REGULATORY HISTORY

Labels and labeling were submitted by the Applicant on May 4, 2009 incorporated the proposed name 'Trelstar' for NDA 022437, along with prior approval supplement (PAS) requests for name changes to currently approved 'Trelstar LA' and 'Trelstar Depot'. Our proprietary name review for these requests (OSE #2009-893, 921 and 920) determined that the proposed name 'Trelstar' was acceptable for NDA 022437 but that PAS name changes for the currently approved products 'Trelstar LA' (NDA 20715/S018) and 'Trelstar Depot' (NDA 21288/S015) were acceptable contingent on the approval of NDA 22-437.

On June 16, 2009, the Division of Drug Oncology Products (DDOP) issued an information request to the Applicant for CMC deficiencies found during the review process of NDA 022437, and on July 10, 2009, DDOP issued a Complete Response letter to the Applicant regarding these deficiencies.

On September 10, 2009, the Applicant responded to the Division's Complete Response letter and subsequently, reviews for all disciplines commenced with a new goal date of March 11, 2010.

On February 3, 2010, the Applicant also submitted an Amendment to the Pending Application including a request for changes to Section 2.1 Dosing Information, with the request to add the word (b) (4) to the currently proposed dosing schedules for all strengths, which is currently presented in 'weeks'.

1.3 PRODUCT INFORMATION

Trelstar (Triptorelin Pamoate) for Injectable Suspension is indicated for the palliative treatment of advanced prostate cancer (b) (4) Triptorelin Pamoate is available in strengths for varying frequency of administration. The 3.75 mg strength (Trelstar Depot) is administered monthly, the 11.25 mg strength (Trelstar LA) is administered every 84 days, and the proposed 22.5 mg strength (proposed name Trelstar) is administered every 24 weeks.

Trelstar 22.5 mg will be supplied two ways, first in a single dose vial with a flip-off seal containing sterile lyophilized Triptorelin Pamoate microgranules, or in the Trelstar MIXJECT single-dose delivery system. The MIXJECT delivery system consists of a vial with a flip-off seal containing sterile lyophilized Triptorelin Pamoate microgranules, a MIXJECT vial adapter, and a pre-filled syringe containing sterile water for injection, USP, 2 mL.

2 METHODS AND MATERIALS

2.1 LABELS AND LABELING

Using Failure Mode and Effects Analysis (FMEA), the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the proposed container labels, insert and carton labeling to identify vulnerabilities that could lead to medication errors. A search of the Adverse Events Reporting System (AERS) Database was performed to assess medication errors for the Trelstar product line and was evaluated in DMEPA labels and labeling reviews (OSE #2009-918 and 2009-919). No relevant cases were retrieved, thus, we did not perform a search for this review.

For this product the Applicant submitted labels and labeling on May 4, 2009, June 29, 2009* and February 3, 2010** for review
(See Appendix A through D):

- Container label: Trelstar 22.5 mg vial
- Carton labeling: Trelstar 22.5 mg MixJect Carton and Vial Carton
- Revised Communication and Marketing Plan for Trelstar Proprietary Name Change with Dear Doctor Letter
- Package Insert Labeling* (no image)
- February 3, 2010 Amendment to Pending Application** (no image)

3 RESULTS AND DISCUSSION

We reviewed the labels and labeling originally submitted by the sponsor in May 4, 2009, and find that strength (22.5 mg) is prominently displayed along with the frequency of administration (every 24 Weeks) which should help to differentiate the strength and dosing of this proposed product from the other Trelstar products. We also reviewed draft labeling resubmitted by the Applicant on June 29, 2009, reflecting combined insert labeling for all three Trelstar strengths and find that labeling provides adequate distinction for the dosing of each of the three strengths. Because Trelstar is currently available in a 3.75 mg strength (every four weeks) and a 11.25 mg strength (administered every 12 weeks), both the Division of Drug Oncology Products and DMEPA felt that it was important to provide differentiation through product labels and labeling if all three strengths are managed under the same name, Trelstar. The proposed labels and labeling for Trelstar 22.5 mg provide adequate product distinction through features including the prominent presentation of the product strength and frequency of administration, displayed on the principal display panel, varying color schemes for the three strengths and dosing and administration information in Section 2 of the insert labeling.

On February 3, 2010, the Applicant submitted an Amendment to the Pending Application which included a proposal to add the word (b) (4) to the Section 2.1 Dosing Information, citing precedence with Eligard and Lupron labeling that includes (b) (4), despite study designs which included endpoints measured in days and weeks. Similarly, Trelstar studies measured clinical endpoints in weeks. On February 23, 2010, the DDOP review team met with DMEPA to discuss the Applicant's proposal and agreed that, regardless of prior precedence cited by the Applicant, dosing presentation labels and labeling should remain as originally proposed 'in weeks' and not (b) (4) since the study endpoints were measured in weeks.

DMEPA additionally notes that we find the Applicant's Revised Communication and Marketing Plan helpful in alerting practitioners who already use Trelstar that there is a new strength available, specifically given the pending name change for the two currently marketed products to the single name 'Trelstar'. The sample 'Dear Doctor' letter included in the plan also provides a means of communicating the new product strength through descriptive information about all Trelstar products, along with images of both the new 22.5 mg carton labeling, and the currently marketed 3.75 mg and 11.25 mg strengths, displayed in a side-by-side illustrating the 'discontinued' versus 'new' carton labeling, providing visual reference for health care provider who administer Trelstar in the clinical setting.

4 CONCLUSIONS AND RECOMMENDATIONS

4.1 COMMENTS TO THE DIVISION

DMEPA has reviewed the Applicant's labels and labeling for Trelstar 22.5 mg, and is satisfied that changes implemented by the Applicant adequately address product distinction as discussed during our April 22, 2009 teleconference. DMEPA also concurs with the DDOP decision that given the Applicant's study endpoints were measured in 'weeks', product labels and labeling should also reflect frequency of use in 'weeks', as originally proposed by the Applicant in their June 29, 2009 Response to FDA Changes to Draft Labeling submission. Therefore, we concur with the Division's decision to deny the Applicant's request presented in their February 3, 2010 Amendment to the Pending Application for the addition of the word (b) (4) to the Section 2.1 Dosing Information Table.

DMEPA also notes that we continue to find the proposed proprietary name, Trelstar, acceptable as proposed by the Applicant in their May 4, 2009 Proprietary Name Reconsideration Request. Please refer to our original Proprietary Name Reviews of Trelstar 3.75 mg, 11.25 mg and 22.5 mg (OSE 2009-893, 2009-920 and 2009-921) dated July 22, 2009, where we found the name change acceptable for all strengths, contingent on the approval of NDA 022437.

Since the Applicant has submitted prior approval supplement revisions to container labels and carton labeling and request for name changes for the 3.75 mg and 11.25 mg strengths NDA 020715/018 and NDA 021288/S-015, any decisions regarding approval of those supplements should be simultaneously coordinated with actions made with regard to this pending application. However, if pending NDA 022437 does not get approved, DMEPA will need to reconsider the Applicant's proposal since the timelines for Trelstar LA and Trelstar Depot name changes and PAS label revisions to carton and containers, are contingent on the scheduled PDUFA date for the pending NDA.

We would be willing to meet with the Division for further discussion, if needed. Please copy us on any communication to the sponsor with regard to this review. If you have further questions or need clarifications, please contact Sandra Griffith, OSE Project Manager, at 301-796-2445.

5 REFERENCES

1. Reviews

OSE Review #2008-2046 Proprietary Name Review for Trelstar (Triptorelin Pamoate for Injectable Suspension) 22.5 mg, Miller, C; March 19, 2009.

OSE Review #2009-422 and #2009-424 Prior Approval Supplement Name Change Review for Trelstar Depot and Trelstar LA Triptorelin Pamoate for Injectable Suspension) 3.75 mg and 11.25 mg, Miller, C; March 20, 2009.

3 page(s) of Draft Labeling have been Withheld in Full immediately following this page as B4 (CCI/TS)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22437	ORIG-1	WATSON LABORATORIES INC	TRELSTAR [redacted] (b) (4)

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/s/

CATHY A MILLER
03/02/2010

KELLIE A TAYLOR
03/03/2010

CAROL A HOLQUIST
03/03/2010

SEALD LABELING REVIEW

APPLICATION NUMBER	NDA 22-437
APPLICANT	Watson Laboratories, Incorporated
DRUG NAME	TRELSTAR (triptorelin pamoate for injectable suspension)
SUBMISSION DATE	September 11, 2009
SEALD REVIEW DATE	March 2, 2010
SEALD REVIEWER(S)	Debbie Beitzell, BSN
	This review does not identify all guidance-related labeling issues and all best practices for labeling. We recommend the review division become familiar with those recommendations. This review does attempt to identify all aspects of the draft labeling that do not meet the requirements of 21 CFR 201.56 and 201.57.

20 page(s) of Draft Labeling have been Withheld in Full immediately following this page as B4 (CCI/TS)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22437	ORIG-1	WATSON LABORATORIES INC	TRELSTAR [redacted] (b) (4)

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/s/

DEBRA C BEITZELL
03/02/2010

LAURIE B BURKE
03/02/2010

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: 6/25/09

TO: Kim Robertson, Regulatory Project Manager
Y. Max Ning, Medical Officer
Division of Drug Oncology /Products

FROM: Robert Young
Good Clinical Practice Branch
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch 2
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA: 22-437

APPLICANT: Watson Laboratories, Inc.

DRUG: Trelstar (triptorelin)

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATIONS: TRELSTAR (b) (4) is a luteinizing hormone releasing hormone (LHRH) agonist indicated for the palliative treatment of advanced prostate cancer.

CONSULTATION REQUEST DATE: 16 Jan 09

DIVISION ACTION GOAL DATE: 23 June 09

PDUFA DATE: 12 July 2009

I. BACKGROUND:

Trelstar (triptorelin) is the subject of an approved NDA (year 2000). Presently marketed is a one month and three month formulation. This application would add a six month formulation.

> Protocol DEB-TRI6M-301 was "A multicentre, open, non-comparative, phase III study on the efficacy, pharmacokinetics and safety of two injections of triptorelin embonate 22.5 mg 6-month formulation in patients with advanced prostate cancer."

Two larger enrolling sites were audited for verification of data in support of this application.

II. RESULTS (by Site):

Name of CI **Location**	**Inspection Date**	**Interim Classification**
Dr Johann.H. van Wyk Suite 207 Wilmedpark Hospital Ametis and Marmer Streets Wilkoppies, Klerksdorp 2570 Republic of South Africa	15 – 19 June 09	Pending
Dr Johann Bahlmann 20 Varing Avenue George 6529 Republic of South Africa	22 – 25 June 09	Pending

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Interim = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

NOTE: Findings pertinent to both Dr Johann H. van Wyk and Dr Johann Bahlmann

A 483 was issued to both Drs. Van Wyk and Bahlmann because the eCRF which they used was not in full compliance with FDA regulations as per Part 11. This study was the first in which this eCRF system was used by the sponsor and eCRF issues were discovered in the course of the study and eight versions of the software were installed and used. The protocol instructions were that the investigator was to sign off on the eCRF. In fact the study coordinator signed off.

Dr. Van Wyk (1st inspected) replied that he did not realize he could not delegate the sign off task. He says that he sat next to the study coordinator, checked the records and instructed her to push the button.

The DSI reviewer checked with the sponsor and the sponsor discovered that one of its employees had on query from the CRO monitor, instructed that the study coordinator could sign off. E-mails from 5 Jun 2007 provided by the sponsor confirm this.

The evaluation of this finding, pertinent to both sites, is unlikely to impact data integrity. There is no evidence that the data were compromised.

1. Dr. Johann H. van Wyk

   Note: this summary is based on preliminary communication with the FDA Field Investigator. An inspection summary addendum will be generated and circulated if conclusions change upon receipt and review of the EIR

   a. **What was inspected**: The records of all 23 subjects were reviewed including consent documents, subject eligibility, protocol adherence, adverse event reporting, and endpoints. There were no limitation to the inspection.

   b. **General observations/commentary**: The records were in order, complete, and accurate. No significant deviations were found, other than what is outlined above.

   c. **Assessment of data integrity**: The data appear to be acceptable and reliable in support of the pending application.

2. Dr. Johann Bahlmann

   Note: this summary is based on preliminary communication with the FDA Field Investigator. An inspection summary addendum will be generated and circulated if conclusions change upon receipt and review of the EIR.

   a. What was inspected: The records of all 16 subjects entered and two screen failures were reviewed including consent documents, subject eligibility, protocol adherence, adverse event reporting, and endpoints. There were no limitations to the inspection

   b. General observations/commentary: The records were in order, complete, and accurate. No significant deviations were found, other than what is outlined above.

   c. Assessment of data integrity: The data appear to be acceptable and reliable in support of the pending application.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two clinical site audits were conducted in support of this NDA. Based on preliminary

communication with the field investigator, there do not appear to be any significant issues of concern with respect to data integrity. The data generated from each study site appear to be valid and can be used in support of the application.

As the final classifications are pending, an addendum to this clinical inspection summary will be forwarded to the review division should there be a change in the final classification or additional observations of clinical and regulatory significance are discovered after reviewing the EIRs

{See appended electronic signature page}

Robert Young
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

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/s/

Robert Young
6/25/2009 06:47:50 PM
MEDICAL OFFICER

Tejashri Purohit-Sheth
6/29/2009 07:54:51 AM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-437

INFORMATION REQUEST LETTER

Watson Laboratories, Inc.
Attention: Wendy DeSpain
577 Chipeta Way
Salt Lake City, UT 84108

Dear Ms. DeSpain:

Please refer to your new drug application (NDA) dated September 12, 2008, submitted pursuant to section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act, for triptorelin pamoate for injectable suspension.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. DMFs (b) (4), 8084 and (b) (4) have been reviewed and found deficient. Letters detailing the deficiencies have been sent to the designated agents for each DMF holder. This application cannot be approved until these deficiencies have been resolved.

2. Regarding the analytical method for drug substance testing:
   a. Either revise the description of methods 02-002264 (peptide assay and identity) and 02-002878 (related substances) to indicate that the sample and reference standard solutions are to be used immediately or revise their method validation studies to address sample stability under room temperature and freezer conditions.
   b. For method 02-002651 (pamoic acid assay and identity), describe the preparation of the drug sample for analysis.
   c. For method 02-002878 (related substances), revise the validation study to address method robustness.

3. The (b) (4) are stated to be part of an on-going extractables/leachables study of the proposed stopper with the proposed drug product. Explain what part of this study has yet to be completed and submitted to the application.

4. Regarding the proposed manufacturing and control sites:
   a. (b) (4) is cited in the application as performing stability testing on Sterile WFI Syringes, and (b) (4) is cited as performing Water Content testing on drug product. Both sites have indicated to the Office of Regulatory Affairs that they do not perform these functions. Clarify the functions performed at these two sites and identify the sites which do perform these functions.
   b. Identify the site for the secondary packaging of the vial-alone configuration.

5. Regarding the drug product manufacturing process:
   a. Provide a list of manufacturing equipment for each processing step and include the intermediate storage containers.
   b. Describe the in-process control for determining completion of the (b) (4) process.
   c. For the manufacture of (b) (4) microgranules, either justify the proposed (b) (4) maximum storage time or provide long term stability data supporting the proposed storage time and condition.
   d. Provide a brief description of the parameters and procedures for the sterilization and depyrogenation of vials and stoppers.
   e. For the filling and microgranule dispersion processes, specify the sampling frequency for weight checks, and describe the weight adjustment procedure used during microgranule dispersion.
   f. Provide a brief description the WFI preparation process and controls, and include the sampling frequency.

6. Regarding the proposed analytical method for drug product testing:
   a. In the validation study for method 02-002236 (Triptoreline Identity, Assay and Content Uniformity), the acceptance criteria for the sample storage studies indicate that you are willing to accept a (b) (4) assay loss for sample held at room temperature for 24 hours in addition to a potential (b) (4) assay loss for sample held at -20°C for 10 days. This is a very large assay loss and a lot which fails assay after being held at -20°C then at room temperature cannot be re-tested or re-sampled. Justify the proposed acceptance criteria for the room temperature study. Also, address method specificity for samples held at -20°C and at room temperature.
   b. Revise the validation study (validation report 02-002550/01) for related substances method 02-002232 to address the (b) (4) impurity. For the specificity study, identify the peaks of each impurity and degradation product observed.

7. Provide a justification for the proposed criteria for Total Impurities, (b) (4) Impurity and Individual Unspecified Impurities based on manufacturing capability and drug product quality with the impurity at the proposed limit.

8. Provide the specifications for the acceptance of vial, stoppers and overseals at the drug product manufacturing site.

9. Regarding the proposed protocol for post approval stability studies:
   a. There is only a limited amount of stability history for the proposed drug product. Therefore, the on-going studies for each of the 5 primary study lots and the 5 supportive study lots need to be completed. In addition, include the 3 month and 9 month sampling sites in the protocol for physical and chemical testing.
   b. Confirm that sterility testing will be performed annually in each of the on-going and post approval stability studies.

10. Regarding the submitted stability information:
   a. There is insufficient data from the primary and supportive stability studies to support the proposed 36 month expiration dating period with storage at USP controlled room temperature. Either provide additional data from these studies or propose a reduced expiration dating period for the drug product.
   b. In the Reconstituted Suspension Study, describe what the “peptide released” test is intended to measure, and how the samples were prepared.

If you have any questions, call Deborah Mesmer, Regulatory Health Project Manager, at 301-796-4023.

Sincerely,

{See appended electronic signature page}

Sarah C. Pope, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Sarah Pope

6/16/2009 04:56:37 PM

DRUP CONSULT: Request for Clinical Evaluation of the Castration Rates of Trelstar (Triptorelin 22.5 mg)

Date: May 20, 2009

To: DURP

Through: Y. Max Ning, MD, Clinical Reviewer, DDOP

Robert Justice, MD, Division Director, DDOP

From: Kim Robertson, CSO, DDOP

Subject: **Request for clinical evaluation of the castration rates demonstrated with Trelstar, a new formulation of triptorelin 22.5 mg.**

I. General Information

Application#: NDA-22-437
Sponsor: Watson Laboratories, INC
Drug: Triptorelin Pamoate for Injectable suspension 22.5
NME: No
Standard Review
Study Population: adults with prostate cancer

II. Background Information

Triptorelin is a GnRH receptor agonist. Its 1-month (3.75 mg) and 3-month (11.25 mg) formulations were approved in 2000 and 2001, respectively, and have been marketed in the United States and Europe for treatment of patients with advanced prostate cancer. Based on the initial review and label, the medical castration (testosterone <1.735 nM) rates related to their approval are summarized in Table 1.

Table 1: Medical Castration Rates related to the approved Trelstar products

	Trelstar Depot (3.75 mg)	**Trelstar LA (11.25 mg)**
Castration rate on Day 29	91.2%	97.7%
Castration maintenance rate (Day 57-253)	96.4%	94.4%

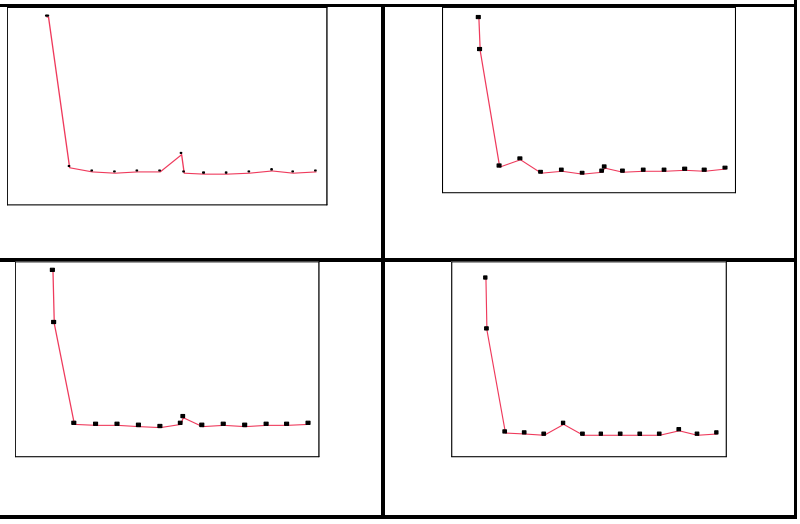
Note: no 95% intervals were found

The sponsor has developed a new triptorelin embonate formulation, designed to release triptorelin over a period of 6 months. Its efficacy and safety were based on an open-label, uncontrolled Phase 3 study that enrolled 120 patients with advanced prostate cancer who received two intramuscular injections of the preparation at an interval of 6 months after study initiation. The primary objective was to demonstrate that Trelstar 22.5 mg is effective in achieving medical castration (testosterone <1.735 nM) on Day 29 and in maintaining the suppression from month 2 to month 12. The results are shown in Table 2. The result of a sensitivity analysis is also listed as shadowed. The sensitivity analysis was performed for the maintenance phase through treating 4 patients with an isolated testosterone escape (between 1-2 folds of 1.735 nM) as successful castration. The testosterone diagrams of the 4 patients are shown in Table 3.

Table 2: Medical Castration Rates demonstrated with the current Trelstar 22.5 mg NDA

	Trelstar 22.5 mg ITT (N=120)	**A sensitivity analysis:** Trelstar 22.5 mg ITT (N=120)
Castration rate on Day 29 (95% CI)	97.5% (92.8%; 99.5%)	Not Applicable
Castration maintenance rate (Day 57-253) (95% CI)	93.3% (88.1%; 97.3%)	96.7% (91.7%; 99.3%)

Table 3: Time course diagram of testosterone levels in patients with one isolated escape of no more than 3.5 nM



The testosterone information with time is showed in the following table. The four patients with one isolated escape are labeled in pink, and the two not included are labeled in red and were not included in the sensitivity analysis as they had higher escapes.

Day	(ID 06402)	06604	(ID 06608)	08604	11606	13613
0	35.581	14.113	9.381	28.201	23.36	40.591
1	22.423	14.112	14.195	18.867	18.522	27.553
29	1.19	0.774	0.668	0.828	1.303	1.108
57	0.625	0.398	0.333	0.611	2.333	0.706
85	0.841	0.339	0.451	0.59	0.447	0.46
113	0.663	0.385	6.119	0.365	0.756	3.354
141	0.546	0.393	0.252	0.307	0.316	0.469
169	0.374	1.938	0.373	0.753	0.551	0.648
171	0.787	0.328	1.625	1.966	1.231	.
197	0.902	0.176	0.456	0.377	0.629	0.522
225	0.797	0.219	0.272	0.613	0.699	0.653
253	0.656	0.338	0.442	0.49	0.658	0.463
281	0.769	0.471	0.724	0.664	0.894	1.553
309	0.836	0.338	0.275	0.683	0.652	0.486
337	42.047	0.382	0.388	0.801	1.077	0.792

III. Questions for Consultation

1) Relevant to the medical castration rates demonstrated by the two approved Trelsatr products, are the medical castration rates demonstrated in the Trelstar 22.5 mg application sufficient for approval?

2) The medical reviewer does not think that one isolated testosterone escape with a magnitude of >1.735 but <3.5 nM during the 48 weeks study period is clinically meaningful, since the magnitude still is considerably low as compared to the level for a confirmation of hypogonodism (<6.9 nM or 200 ng/dL). Technically, the castration cut-off of <1.735 nM or 50 ng/dL is relatively arbitrary, not well evidenced with large studies. Based on the Pub-med literature, not all patients who had successful orchiectomy had testosterone levels below 1.735 nM or 50 ng/dL. In addition, there might be other reasons for the blip observed in the patients. In the current case, the timing of the escape did not appear to relate to any incidence of adverse reactions or disease worsening in the patients. Therefore, the reviewer considers the sensitivity analysis result as shown above may represent an acceptable castration maintenance rate of the new formulation, appropriate for consideration in regulatory decision-making for the product. Please comment on the phenomena of minimum isolated testosterone escape and its clinical and regulatory relevancies.

Should you require any additional information, please contact Kim Robertson (regulatory project manager) at 301-796-1441 or Y. Max Ning (medical reviewer) at 301-796-2321.

Concurrence: (as needed)

Y. Max Ning _____ Medical Reviewer
Ellen Maher_____ Clinical Team Leader
Robert Justice_____ Division Director

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/s/

Robert Justice

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