CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-437

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	March 10, 2010
From	Robert L. Justice, M.D., M.S.
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	22-437
Applicant Name	Watson Laboratories, Inc.
Date of Submission	September 11, 2009
PDUFA Goal Date	March 11, 2010
Proprietary Name / **Established (USAN) Name**	Trelstar/ triptorelin pamoate
Dosage Forms / Strength	For injectable suspension / 22.5 mg
Proposed Indication(s)	Palliative treatment of advanced prostate cancer
Action/Recommended Action for NME:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	X
Statistical Review	X (combined clinical and statistical review)
Pharmacology Toxicology Review	X
CMC Review/OBP Review	X
Microbiology Review	X
Clinical Pharmacology Review	X
DDMAC	
DSI	X
CDTL Review	X
OSE/DMEPA	X
OSE/DDRE	
OSE/DRISK	
Other	

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

Signatory Authority Review

1. Introduction

Trelstar (triptorelin pamoate for injectable suspension) is a gonadatropin releasing hormone (GnRH) agonist. This application seeks approval of Trelstar 22.5 mg for administration every 24 weeks for the indication of "palliative treatment of advanced prostate cancer."

The NDA was originally submitted on September 12, 2008. A complete response letter for clinical and CMC deficiencies was issued on July 10, 2009. A complete response to the CR letter was submitted on September 11, 2009. This review will summarize the conclusions and recommendations of each review discipline for both review cycles.

2. Background

Trelstar Depot 3.75 mg (NDA 20-715) is approved for monthly IM injection. Trelstar LA 11.25 mg (NDA 21-288) is approved for administration every 12 weeks. Trelstar 22.5 mg is intended to allow for every 24 week administration. As will be discussed in the Clinical Review and CDTL Review, approvals of GnRH agonists and antagonists have been traditionally based on the achievement and maintenance of castrate levels of testosterone.

3. CMC/Device

First review cycle

The Chemistry Review of 6/16/09 made the following recommendations and conclusion on approvability.

A. RECOMMENDATION & CONCLUSION ON APPROVABILITY

The application CANNOT BE APPROVED from the Chemistry, Manufacturing and Controls (CMC) perspective based on major deficiencies in the application. An acceptable and complete response to the following deficiencies is needed before approval can be recommended from a CMC perspective.

The deficiencies are summarized as follows (see exact wording to be conveyed at end of the review):

1. DMFs (b) (4) 8084 (WFI syringes) and (b) (4) are not adequate. Deficiency letters have been sent to the agent for each file.
2. Additional information is requested on the drug substance analytical methods.
3. Additional information is requested on the stopper extractables/leachables study.
4. Clarification is requested regarding the responsiblities for the proposed manufacturing and control sites.
5. Additional information is requested regarding the drug product manufacturing process.
6. Additional information is requested regarding the validation studies for the drug product analytical methods.
7. Revision and justification is requested for the proposed drug product specification for impurities.
8. Acceptance specifications for the drug product packaging components have been requested.
9. Revisions are requested for the proposed protocol for post approval stability studies.
10. The stability information supporting the proposed expiry period and label storage statement is not adequate.
11. Revisions are requested for the CMC sections of the proposed labels and labeling.

In addition, an overall recommendation has yet to be provided by the Office of Compliance on the proposed manufacturing and control sites, and the microbiology review is currently pending.

The Product Quality Microbiology review of 7/19/09 recommended approval. However, see final CMC recommendation below for further discussion.

The final CMC recommendation of 7/9/09 on this NDA is quoted below.

NDA 22-437 (triptorelin pamoate for injection suspension, 22.5 mg) was initially submitted on 12-SEP-2008 and was granted a standard review by the Agency. Chemistry Review #1 (dated 16-JUN-2009) identified eleven (11) Chemistry, Manufacturing and Controls (CMC) deficiencies which were subsequently communicated to the Applicant. These deficiencies have not been resolved to date. At the time of the Chemistry Review, a final recommendation from the Office of Compliance had not yet been issued, and the microbiology review was not completed.

This memo serves to update that determination. The microbiology review recommends approval of this NDA and was finalized on 19-JUN-2009. However, the Office of Compliance issued an overall withhold recommendation for this application on 07-JUL-2009.

Several CMC deficiencies were conveyed to the Applicant in a 16-JUN-2009 letter. While the majority of these items remain as outstanding CMC issues, two (5d and 9b) were partially covered as part of the subsequent microbiology review dated 19-JUN-2009. Therefore, these two deficiencies were discussed in an informal teleconference on 08-JUL-2009 (Dr. J. McVey, Dr. V. Pawar, Dr. S. Pope, and Dr. M. Adams participating). As a result of that discussion, a decision was made to slightly revise deficiency 5d to read "Verify that the procedures and parameters for the sterilization and depyrogenation of vials and stoppers in this application are the same as those validated and approved in NDA 20-715 and NDA 21-288." Additionally, the participants collectively decided to delete deficiency 9b, as it was already covered by the microbiology review. These revisions were made in the action letter language.

Three of the proposed manufacturing sites received withhold recommendations from the Office of Compliance. While only one of the sites (Debio) was actually inspected, all three sites (Debio, (b) (4) will be mentioned in the action letter as having received withhold recommendations.

NDA 22-437 has outstanding CMC deficiencies, as well as an overall withhold recommendation from the Office of Compliance. Accordingly, from a CMC perspective, approval of NDA 22-437 cannot be recommended until any related deficiencies are resolved.

Second review cycle

The Chemistry Review of 3/3/10 stated that "The application is APPROVABLE from the Chemistry, Manufacturing and Controls (CMC) perspective pending final OC Overall Conclusion of "acceptable" (revised conclusion is awaiting the results of a GMP inspection at a drug product manufacturing site) and a minor labeling revision." The proposed expiry period of 36 months was found to be acceptable.

The Branch Chief Memorandum of 3/8/10 provided a final update on the status of the CMC review. The memo stated that "Acceptable labeling (PI, container/carton labels) was submitted by the Applicant on 03-MAR-2010, and an acceptable recommendation was received from the Office of Compliance on 08-MAR-2010." The memo concluded that "There are no outstanding CMC issues for this NDA, and this NDA is now recommended for approval from the CMC perspective."

I concur with the conclusions reached by the chemistry reviewers regarding the approval action on this NDA.

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology Review from the first cycle is quoted below.

> NDA 22-437 does not contain any new information on the toxicology of the product. Three pharmacokinetic studies have been submitted, indicating decreased levels of testosterone in response to the new formulation of triptorelin. The NDA relies on pharmacology and toxicology information submitted for triptorelin pamoate under NDA 20-715. There are no formulation differences that would be expected to change the pharmacological or toxicological activity between previous formulations and the formulation that is being proposed under NDA 22-437. Only the duration of activity should be expected to change. One of the excipients, (b) (4) Poly(D,Llactide-coglycolide), is a novel polymer in this formulation but the DMF relied upon (DMF (b) (4) has been reviewed and relied upon for approved products in the past (significantly, it has been referred to for NDA 021731, an approved 6-month depot formulation of 45 mg leuprolide acetate). Furthermore, there is no change in proposed indication (palliative treatment of advanced prostate cancer). Given these facts, the pharmacology/toxicology review conducted for NDA 20-715 is sufficient and an additional pharmacology and toxicology review for this NDA is not needed.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that an additional pharmacology and toxicology review is not needed.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology Review of 6/18/09 provided the following executive summary and recommendations.

The Applicant seeks approval of NDA 22-437 for **TRELSTAR 6-MONTH** (triptorelin pamoate injectable suspension) **22.5 mg** (6-month sustained-release formulation) to be used as a palliative treatment of advanced prostate cancer. **TRELSTAR 6-MONTH** has the same indication, dosage form (injection), and route of administration (intramuscular) as for the approved triptorelin **3.75 mg** (1-Month) and **11.25 mg** (3-Month) sustained-release formulations.

In support of the efficacy and safety of **TRELSTAR 6-MONTH** (22.5 mg triptorelin injectable suspension) in the advanced prostate cancer indication, the Applicant submitted a pivotal Phase 3 study in 120 patients (**Study 301**). In this study, all patients were given two intramuscular injections of triptorelin pamoate 22.5 mg at an interval of 6 months. The primary efficacy endpoint was to determine the percentage of patients who achieved castration levels of ≤ 0.5 ng/mL on Day 29 and the percentage of patients who maintained these levels from Day 57 through Day 337. The results of the study showed that for the intent-to-treat (ITT) population, 97% (117/120) achieved castration levels of testosterone on Day 29 and 93% (107/115) maintained these throughout study treatment.

The pharmacokinetics (PK: serum triptorelin) and the pharmacodynamics (PD: serum testosterone) were evaluated in a subset of **15 patients** in the pivotal **Study 301** after the **6-month formulation**. Fourteen patients (14/15, 93%) achieved castration **testosterone** serum levels of ≤0.5 ng/mL at **Day 29** and maintained these levels at **Days 57-337**. One patient did not maintain castration testosterone levels during this period. The 6-Month formulation of triptorelin was found to be at least as effective as the approved 1-month and the 3-Month formulations in achieving and maintaining castration level of testosterone.

1.1 RECOMMENDATIONS

The Office of Clinical Pharmacology has reviewed the information contained in NDA 22-437 and found it acceptable from the clinical pharmacology perspective.

I concur with the conclusions reached by the clinical pharmacology reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

The following summary of the study design and efficacy results are from the agreed-upon package insert.

> TRELSTAR 22.5 mg was studied in a non-comparative trial of 120 men with advanced prostate cancer. The clinical trial population consisted of 64% Caucasian, 23% Black, and 13% Other, with a mean age of 71.1 years (range 51-93). The response to triptorelin was comparable between racial groups. Patients received TRELSTAR 22.5 mg (N = 120) every 24 weeks for a total of 2 doses (maximum treatment period of 337 days). The primary efficacy endpoint included achievement of castration by Day 29 and maintenance of castration from Day 57 through Day 337.

Castration levels of serum testosterone (≤ 1.735 nmol/L; equivalent to 50 ng/dL) were achieved at Day 29 in 97.5% (117 of 120) of patients treated with TRELSTAR 22.5 mg. Castration was maintained in 93.3% of patients in the period from Day 57 to Day 337.

A summary of the clinical studies for TRELSTAR is provided in Table 7.

Table 7. Summary of TRELSTAR Clinical Studies

Product Strength	**3.75 mg**	**11.25 mg**	**22.5 mg**
Number of Patients	137	171	120
Treatment Schedule	every 4 weeks	every 12 weeks	every 24 weeks
Duration of Study	253 days	253 days	337 days
Castration Rate [a] on Day 29, % (n/N)	91.2% (125/137)	97.7% (167/171)	97.5% (117/120)
Rate of Castration Maintenance[b] from Days 57 – 253, %	96.2%	94.4%	Not applicable
Rate of Castration Maintenance from Days 57 – 337, % (n/N)	not applicable	not applicable	93.3% (112/120)[c]

[a] Maintenance of castration was calculated using a frequency distribution.

[b] Cumulative maintenance of castration was calculated using a survival analysis (Kaplan-Meier) technique.

[c] Calculation includes 5 patients who discontinued the study but who had castrate levels of testosterone prior to discontinuation.

First review cycle

The combined Clinical and Statistical Review made the following recommendation on regulatory action during the first cycle.

> Watson Pharmaceuticals submitted the TRELSTAR (triptorelin 22.5 mg) application, NDA 22-437, on September 12th, 2008, and requested marketing approval of this new formulation for the treatment of patients with advanced prostate cancer.
>
> Based on the data submitted and the analysis results obtained from our review, we found that the application has provided adequate evidence to support the efficacy and safety of the new triptorelin 22.5 mg formulation for use in the intended patient population at the proposed dosing schedule. Therefore, the reviewers recommend regular approval of the new formulation for the treatment of patients with advanced prostate cancer, provided that all issues raised by the other review disciplines have been addressed satisfactorily.
>
> It is necessary to point out that approximately 28% of patients in the key study supporting this NDA had biochemical relapse only disease with no evidence of metastasis. Since the disease setting generally is not recognized as advanced disease and since androgen deprivation in this setting has not been proven beneficial, the inclusion of these patients in the developmental study does not constitute a basis for or implied use of the new formulation in patients with biochemical relapse only disease in routine practice.

The Cross-Discipline Team Leader Review summarized the clinical issues with this application in the following excerpt from the Risk Benefit Assessment.

> This product will provide increased patient and physician convenience by extending the interval between treatments. Its adverse event profile is consistent with that seen in previous studies of GnRH agonists in prostate cancer. The risks of this product are primarily related to its efficacy. Using the analyses specified in the Statistical Analysis Plan, castrate testosterone levels were achieved in 93% (86.8%; 97.0%) of patients using the LC/MS testosterone levels. This is consistent with previous GnRH approvals. However, castrate testosterone levels were achieved in 80.2% (72.0%; 87.0%) using the immunoassay testosterone levels. Other approved products are available for use at 24
>
> week intervals for this indication. In order to not subject patients to a less efficacious product, it will be important to establish that this product provides comparable efficacy prior to its approval.

The review recommended that the following comments be sent to the applicant.

1. For Study DEB-TRI6M-301, you have provided testosterone levels using two difference assay methods, immunoassay and liquid chromatography/tandem mass spectroscopy (LC/MS). The result of the analysis of the co-primary endpoint, maintenance of castrate testosterone levels from Day 57 to Day 337, using testosterone levels derived from the immunoassay differs markedly from the result using testosterone levels derived from the assay using LC/MS. It is unclear whether the co-primary endpoints should be analyzed using the results of the immunoassay or of LC/MS.

    a. Please provide your rationale for the use of testosterone levels from the LC/MS assay in your primary analyses. Please compare the testosterone assay used in your primary analysis to the methods used to assay testosterone levels in your own licensure applications, in the licensure applications of others and in published articles.
    b. Please provide references to support your contention that the LC/MS method is preferred for the assay of hypogonadal testosterone levels. This should include a comparison of the intra-assay and inter-assay coefficient of variation using both of these assay methods.
    c. Please provide information concerning the storage and shipment conditions used for the testosterone serum samples.

Based on their prior experience with GnRH agonists, a consult was obtained from the Division of Reproductive and Urologic Products during the first review cycle. The DRUP responses to two questions and an additional comment are quoted below.

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

Response: For the Trelstar 22.5mg analyses shown, the testosterone values used were those obtained with the LCMS method of the central laboratory in the (b) (4) (b) (4) not those obtained with the automated (b) (4) immunoassay used in the local central laboratory in the (b) (4) If one considers just the (b) (4) testosterone values, then the percentages of successful "achievers" and "maintainers" in the current Trelstar NDA are comparable to those reported in the previous Trelstar applications as well as those reported for other approved products. See our Additional Comment below.

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 week study period is clinically meaningful, since the magnitude is still considerably low as compared to the level for a confirmation of hypogonadism (< 6.9 nM or 200ng/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 may represent an acceptable castration rate of the new formulation, appropriate for consideration in regulatory decision-making for the product. Please comment on the phenomenon of minimum isolated testosterone escape and its clinical and regulatory relevancies.**

Response: Using the testosterone values obtained from (b) (4) there are 6 individual "non-maintainers" who had single isolated T levels > 1.735 nmol/L and two additional "non-maintainers" who had more than one T level >1.735 nmol/L. Four of these patients show an isolated "low grade" escape (T level between 1.735 nmol/L and 3.5 nmol/L). We agree that it is reasonable for clinical judgment to play a role in the assessment of these cases.

3. Additional Comment

We note that the submission contains two complete sets of testosterone data, one from (b) (4) (b) (4) immunoassay method) and one from (b) (4) (b) (4) LCMS method). On page 29 of 378 of the Clinical Study Report (CSR) for DEB the Sponsor states:

> "*Serum testosterone levels were measured in two central laboratories (Quintiles Laboratories in the Republic of South Africa, and Medeval Limited laboratory in the United Kindom).*
>
> *The local central laboratory on the* (b) (4) *[automated immunoassay,* (b) (4) *LOQ 0.35 nmol/L]) provided the Investigators with values for the daily follow-up of the patients, and these local laboratory values were also used to assess the eligibility of the patients for the study.*

However, it is known that the routine assays particularly in the hypogonadal testosterone range have poor precision. The [(b) (4)] method used by [(b) (4)], although validated, has shown a positive bias (overestimation of the testosterone values) when compared with the reference method, the liquid chromatography/tanden mass spectrometry [LC/MS], which has been validated especially for the low hypogonadal range [Reference 6]. Therefore, Debiopharm decided to have back-up samples for each testosterone sample analyzed with the more cumbersome but also more accurate LC/MS method to double-check the [(b) (4)] values. In all the analyses other than those regarding the inclusion of the patients, testosterone values obtained with the LC/MS of the central labeloratory in the [(b) (4)] were used ([(b) (4)] and LC-MS/MS analyses, LOQ 0.1 nmol/L (30 pg/ml), section 16.1.10])."

While this reasonable explanation was provided in the CSR, we find nothing in the protocol or protocol amendments to this end. The Sponsor states that the [(b) (4)] assay was prone to higher T levels (due to "overestimation"), and it appears true that the T levels were higher for the [(b) (4)] data compared to the [(b) (4)] data. It is clear that an analysis of the [(b) (4)] data would show lower percentages of success for both "achieve" (perhaps 93%) and "maintain" (perhaps 82%) compared to the same analysis of the [(b) (4)] data. This issue raises several questions, but in our view, the key question is: Which assay methodology more accurately reflects a castrate T level (≤ 1.735 nmol/L)?

Second review cycle

The Medical Officer Review of 2/19/10 concluded the following.

> In the reviewer's opinion, the applicant has satisfactorily addressed the clinical deficiencies as listed in the CR letter. The applicant's responses do not affect the original clinical review findings and conclusions dated June 29, 2009. Therefore, the reviewer recommends regular approval of the TRELSTAR 22.5 mg formulation for the treatment of patients with advanced prostate cancer."

The CDTL Memo of 3/5/10 summarized the applicant's responses to the clinical deficiencies.

1. **For Study DEB-TRI6M-301, you have provided testosterone levels using two different assay methods, immunoassay and liquid chromatography/tandem mass spectroscopy (LC/MS). The result of the analysis of the co-primary endpoint, maintenance of castrate testosterone levels from Day 57 to Day 337, using testosterone levels derived from the immunoassay differs markedly from the result using testosterone levels derived from the assay using LC/MS. It is unclear whether the co-primary endpoint should be analyzed using the results of the immunoassay or of LC/MS.**

    a. **Please provide your rationale for the use of testosterone levels from the LC/MS assay in your primary analyses. Please compare the testosterone assay used in your primary analyses to the methods used to assay testosterone levels in your own approved applications, in the approved applications of others (reviews available on the FDA website) and in published articles.**

The applicant included references to support the use of the LC/MS method as the gold standard for detection of testosterone levels in the hypogonadal range. The applicant stated that a decision was made; prior to study conduct, to use the results of the LC/MS testosterone assay in the primary analysis. This is supported by the availability of samples and storage records for all patients.

The applicant summarized the assays used during previous approvals of GnRH agonists. They also provided a general comparison of RIA (previous Trelstar approvals used RIA) and LC/MS from the International Interlaboratory Quality Control Scheme for Steroid Hormones. The data suggests that the correlation coefficient is quite high (0.994) and that the intercept approaches zero (-0.063 nmol/L). This suggests that the parameters for the percentage of patients who achieve castrate testosterone level should be similar between trials which use RIA and those that use LC/MS.

b. Please provide references to support your contention that the LC/MS method is preferred for the assay of hypogonadal testosterone levels. This should include a comparison of the intra-assay and inter-assay coefficient of variation using both of these assay methods.

As stated above, the applicant provided references to support their contention that the LC/MS method is the gold standard when assaying low testosterone concentrations. The applicant also provided a comparison of the assay characteristics for LC/MS and the immunoassay method (see primary review). The data suggests that the assays have similar inter- and intra-assay coefficients of variation, but that the immunoassay has a positive bias in the estimation of testosterone levels. To support this, the applicant again provided data from the International Interlaboratory Quality Control Scheme for Steroid Hormones. This data suggest that immunoassay overestimates testosterone levels by 0.47 nmol/L when compared to LC/MS.

c. Please provide information concerning the storage and shipment conditions used for the testosterone serum samples.

Since the results of the testosterone analysis by LC/MS (b) (4) (b) (4) were lower than those by obtained by immunoassay in (b) (4) it was possible that these samples had degraded during shipment or storage. The applicant was, therefore, asked for information on the shipment and storage of their samples. Sample shipping appeared adequate. However, the mean time between sample collection and receipt in the laboratory was 1.04 $\pm$ 0.69 days and additional comments could not be made concerning the rapidity of sample handling in the laboratory since time was recorded in days. Sample storage was adequate and information was provided on testosterone degradation under various storage conditions.

The CDTL Review concluded that "Watson Laboratories has adequately addressed the issues raised in the complete response letter and I recommend approval of Trelstar 22.5 mg."

I concur with the recommendations for approval made by the clinical team.

8. Safety

The treatment-emergent adverse events reported in ≥ 5% of patients are shown in Table 4.

Table 4. TRELSTAR 22.5 mg: Adverse Reactions Reported by 5% or More of Patients During Treatment

Adverse Reactions[1]	TRELSTAR 22.5 mg N = 120			
	Treatment-Emergent		Treatment-Related	
	N	%	N	%
General Disorders and Administration Site Conditions				
Edema peripheral	6	5.0	0	0
Infections and Infestations				
Influenza	19	15.8	0	0
Bronchitis	6	5.0	0	0
Endocrine				
Diabetes Mellitus/Hyperglycemia	6	5.0	0	0
Musculoskeletal and Connective Tissue Disorders				
Back pain	13	10.8	1	0.8
Arthralgia	9	7.5	1	0.8
Pain in extremity	9	7.5	1	0.8
Nervous System Disorders				
Headache	9	7.5	2	1.7
Psychiatric Disorders				
Insomnia	6	5.0	1	0.8
Renal and Urinary Disorders				
Urinary tract infection	14	11.6	0	0
Urinary retention	6	5.0	0	0
Reproductive System and Breast Disorders				
Erectile dysfunction	12	10.0	12	10.0
Testicular atrophy	9	7.5	9	7.5
Vascular Disorders				
Hot flush	87	72.5	86	71.7
Hypertension	17	14.2	1	0.8

[1]Adverse reactions for TRELSTAR 22.5 mg are coded using the Medical Dictionary for Regulatory Activities (MedDRA)

The size of the safety database and the safety profile is similar to that of other GnRH agonists that have been approved.

9. Advisory Committee Meeting

This application was not taken to an Advisory Committee.

10. Pediatrics

A pediatric waiver was granted by PeRC.

11. Other Relevant Regulatory Issues

The DSI Clinical Inspection Summary stated the following.

> Two clinical site audits were conducted. 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.

12. Labeling

- Proprietary name: In their consultation of 3/19/09, DMEPA objected to changing the names Trelstar Depot and Trelstar LA to Trelstar because of the potential for medication errors. In a telecon with the applicant on 4/22/09, it was agreed that the applicant could submit a revised integrated package insert that reflects information on all three strengths.

- Physician labeling: Agreement has been reached on the integrated physician labeling.

- Carton and immediate container labels: Agreement has been reached on the carton and container labels.

- Patient labeling/Medication guide: none.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Approval

- Risk Benefit Assessment: The efficacy and safety of this product is similar to that of other approved GnRH agonists and the risk benefit assessment is favorable for the palliative treatment of patients with advanced prostate cancer.

- Recommendation for Postmarketing Risk Management Activities: None

- Recommendation for other Postmarketing Study Commitments: None

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/

ROBERT L JUSTICE
03/10/2010