

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-437

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	February 19, 2010
From	V. Ellen Maher, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 22-437
Applicant	Watson Laboratories
Dates of Submission	9/12/2008; 9/10/2009
PDUFA Goal Date	3/11/2010
Proprietary Name / Established (USAN) names	Trelstar/ Triptorelin pamoate
Dosage forms / Strength	Intramuscular sustained release/22.5 mg
Proposed Indication(s)	Advanced, (b) (4) Prostate Cancer
Recommended:	Approval

1. Introduction

Watson Laboratories submitted NDA 22-437 on September 12, 2008. The application requested approval of a new formulation and dose of triptorelin administered every 24 weeks. The application is supported by a single arm study, DEB-TRI6M-301. This study protocol was submitted in April of 2006 and the study was conducted from July 2006 to August 2007. The final statistical analysis plan was submitted in March 2007. There are currently two approved triptorelin formulations; 3.75 mg every 4 weeks and 11.25 mg every 12 weeks.

The initial application received a complete response letter asking them to address the following deficiencies.

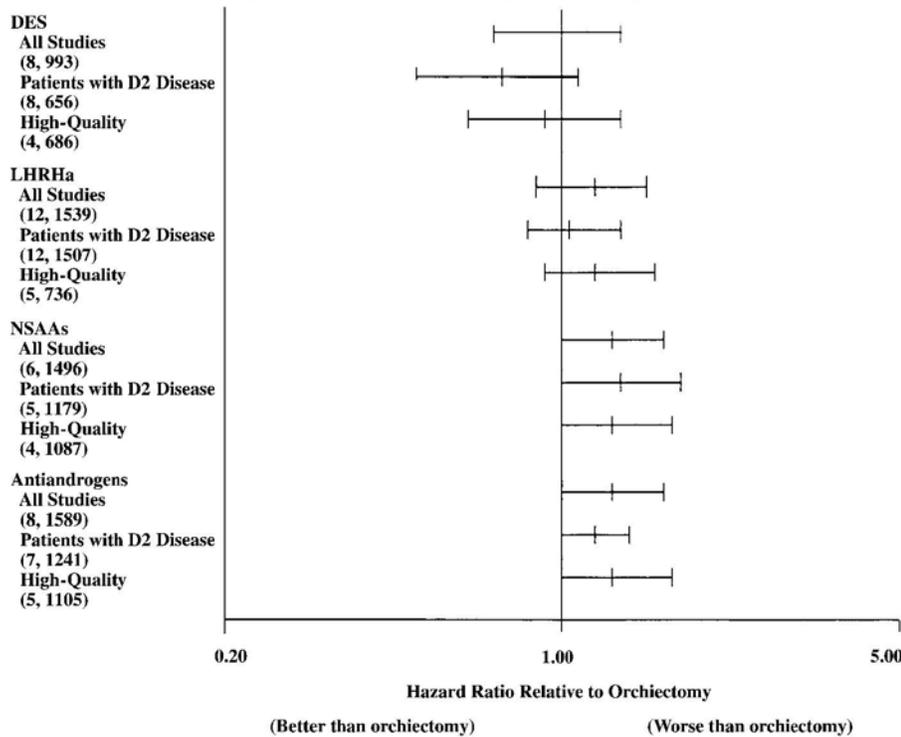
- Deficiencies were found in several Drug Master Files. Further, Debiopharm, the drug product manufacturer, has failed GMP inspection and on inspection, the responsibilities of the various contract laboratories are unclear. Additional sites may require inspection.
- The co-primary endpoints of DEB-TRI6M-301 are based on testosterone levels. The applicant has used two assay methods to measure serum testosterone. Analysis of the co-primary endpoints using the testosterone levels from the first assay resulted in a markedly different conclusion than the use of testosterone levels from the second assay. The difference is enough to affect the approvability of this product. It is unclear which assay results should be used in the primary analysis.

The comments included in the complete response letter and the applicant's responses to these comments follow the initial review.

2. Background

GnRH (gonadotropic releasing hormone) agonists cause a transient surge in luteinizing hormone (LH), follicle stimulating hormone (FSH), and testosterone. This surge desensitizes the LH and FSH receptors and is followed by a sustained decrease in testosterone to levels comparable to orchiectomy. Prostate cancer is a hormone responsive disease and testosterone withdrawal results in tumor shrinkage. However, patients who cannot tolerate the initial surge in testosterone (and resultant increase in tumor mass) should not receive a GnRH agonist. This includes patients at risk of spinal cord compression or ureteral obstruction. Over time, tumors can become hormone independent and no longer respond to testosterone withdrawal. Nonetheless, portions of the tumor remain hormone sensitive and GnRH agonists are typically continued in these patients.

Because GnRH agonists act by causing a decrease in serum testosterone, the ability to induce castrate levels of testosterone has been used as a surrogate endpoint for the approval of GnRH agonists and antagonists. Early studies compared GnRH agonists to orchiectomy or DES. Seidenfeld et al have conducted a thorough meta-analysis of these early trials (Ann Intern Med 2000 132(7):566). The outcomes of various methods of chemical castration, in terms of overall survival, are compared to orchiectomy in the figure below.



When GnRH agonists (as a class) are compared to orchiectomy, the hazard ratio for overall survival is 1.262 (95% CI 0.915, 1.386) in favor of orchiectomy. Given this overlap in confidence intervals and increased patient acceptability, GnRH agonists have become the standard of care for the first line treatment of metastatic prostate cancer.

While this addresses overall survival, the use of testosterone levels as a surrogate marker for overall survival is less well documented. Several early studies compared testosterone suppression in patients who received diethylstilbestrol or orchiectomy to those who received a GnRH agonist. In a study of leuprolide versus DES, approximately 100 patients per arm, the time to progression (60 vs. 61 weeks) and degree of testosterone suppression (after the first week) were similar (NEJM 1984 311:1281). In a study of a GnRH agonist versus orchiectomy, approximately 40 patients per arm, suppression of testosterone was present in both arms at one month and was similar between arms (Lancet 1985 2:1201). From these early studies, the testosterone cutoff value (castrate level, non-castrate level) has been determined to be 50 ng/dL or 1.735 nM. Also from these early studies, some variability was seen in the number of patients who attained castrate testosterone levels using orchiectomy or DES. This is, in part, related to the use of pulpectomy rather than orchiectomy and to the inaccuracy of the assay. Therefore, previous approvals have permitted a small percentage of patients to have non-castrate testosterone levels at a limited number of time points. However, the number of assessments (and thus the number of non-castrate levels) has not been standardized. Further, testosterone assay methods have improved since the initial approvals and most current applications use a highly accurate liquid chromatography/mass spectroscopy method (LC/MS).

The pivotal study in this application DEB-TRI6M-301 used two methods to measure testosterone levels, an immunoassay and LC/MS. The protocol stated that levels would be measured centrally, but did not state what method would be used and it is unclear which assay results should be used in the analysis of the co-primary endpoints. Approved GnRH agonists such as Eligard used a method with a 15% inter and intra-assay variability and a lower limit of quantitation (LLQ) of 3 ng/dL. The Lupron approval used a LLQ of 3 ng/dL. The coefficient of variation is not available. Previous Trelstar approvals have used a LLQ of 0.2 nM (5.8 mg/dL). The coefficient of variation is not available. In the current application, the immunoassay has a LLQ of 0.35 nM (10.1 ng/dL) while the LC/MS has a LLQ of 0.105 nM (3.0 ng/dL). The within run coefficient of variation (CV) was 2.3-6.2% (immunoassay) and 8.58% (LC/MS) and the between run CV was 1.4-4.7% (immunoassay) and 8.81% (LC/MS).

3. CMC/Device

A complete response letter will be issued for this application due to unresolved CMC issues. Major deficiencies include the following.

1. Deficiencies were found in Drug Master Files (b)(4) (drug substance), 8084 (water for injection syringe), and (b)(4) (release polymer).
2. Debiopharm, the drug product manufacturer, has failed GMP inspection.
3. The responsibilities of the proposed manufacturing and control sites and the various contract laboratories were found to be unclear or incorrect by the inspectors. Additional sites may require inspection.

Please see the CMC review for additional information concerning these deficiencies.

Triptorelin pamoate is a synthetic decapeptide agonist of GnRH. Triptorelin substitutes a different D amino acid at position 6, increasing resistance to cleavage by proteolytic enzymes

and prolonging the half life when compared to native GnRH. Triptorelin is formed into microgranules by (b) (4). The 24 week formulation administers (b) (4) microgranules to provide a 6 month sustained release (by using different release characteristics). (b) (4). Lyophilized powder is dissolved in 2 mL water for injection and is administered intramuscularly every 24 weeks. The product may be administered using the Mixject device (K963583). The composition of Trelstar 22.5 mg is shown below.

Commercial Formulation-per vial

Triptorelin pamoate	(b) (4)
Poly(d,l lactide-co-glycolide)	(b) (4)
Poly(d,l-lactide co-glycolide)	(b) (4)
Mannitol	(b) (4)
Carboxymethylcellulose sodium	(b) (4)
Polysorbate 80	(b) (4)

4. Nonclinical Pharmacology/Toxicology

Limited nonclinical pharmacology/toxicology studies were conducted with the 24 week formulation and included PK/PD studies used to choose the clinical 24 week formulation of triptorelin pamoate. Local toxicity with the 24 week formulation was not assessed.

Studies of acute and chronic toxicity, genotoxicity, mutagenicity, reproductive toxicity, and local tolerance were included in NDA 20-715, triptorelin 3.75 mg/monthly. Briefly, triptorelin pamoate was not mutagenic in the Ames assay or in CHO cells. However, pituitary tumors and sarcomas were found following long term animal exposure. Further, triptorelin is considered Pregnancy Category X. Male fertility has not been assessed in an animal model.

5. Clinical Pharmacology/Biopharmaceutics

The effect of triptorelin on drug metabolizing enzymes is unknown. Triptorelin is metabolized in the tissues and plasma and is eliminated by both the kidneys and liver. Exposure is increased in patients with moderate to severe renal disease and in those with liver disease. Elimination is delayed in the elderly. This is thought to be due to the decrease in creatinine clearance that occurs with age. In an elderly population with prostate cancer, the C_{max} of the 24 week formulation is 44.1 ng/mL and the AUC 112 ng·h/mL. A QT study has not been performed and a clinical increase in arrhythmias has not been seen.

6. Clinical Microbiology

See the CMC review.

7. Clinical/Statistical- Efficacy

This application is supported by a single arm trial, DEB0TRI6M-301, in which patients received 2 doses of triptorelin 22.5 mg every 24 weeks. This study was submitted in April of 2006 and completed at 13 centers in the Republic of South Africa from July 2006 to August 2007. Prior to this, the applicant conducted a study (N=10) using a different formulation of triptorelin intended for administration every 24 weeks. This study failed to meet its endpoint. The applicant then conducted a second study (N=24; 8 per formulation) using 3 different formulations of triptorelin. One of these formulations was chosen for use in DEB-TRI6M-301. DEB-TRI6M-301 recruited patients with pathologically confirmed adenocarcinoma of the prostate who had locally advanced disease, metastatic disease, or a rising PSA after primary therapy. Patients entering this study had a baseline testosterone level > 5 nM. Patients could not receive hormonal therapy for prostate cancer within 6 months of entry, 5- α -reductase inhibitors within 2 months of entry, and medications which could affect the metabolism and/or secretion of androgenic hormones (ketoconazole, etc.) at the time of entry. Triptorelin 22.5 mg was administered intra-muscularly on Days 1 and 169. Testosterone levels were obtained monthly and PSA was collected every 3 months.

Patient Disposition

Patient Disposition ¹	
Patient Disposition	Triptorelin 22.5 mg N = 120
Patients Enrolled	120
Patients Who Received Study Drug	120
Completed the Study	115
Discontinued	5
Death	3
Lost to Follow Up 01602	1
Patient Decision 13606	1

¹This table is derived from the primary review.

Triptorelin 22.5 mg was administered IM to 120 patients on Day 1. One patient died on Day 85 and triptorelin 22.5 mg was administered to 119 patients on Day 169. The 3 patients who died on study and the 2 who discontinued are discussed in the safety section. All had castrate testosterone levels at their last assessment.

Disease Characteristics

The table below provides the baseline disease characteristics of the 120 patients enrolled in DEB-TRI6M-301. The median age was 69.9 years and 64.2% were white, 22.5% black, and 13.3% colored (NOS).

Baseline Disease Characteristics ¹	
Baseline Characteristic	N = 120
Disease Stage	
Metastatic Disease	10 (8%)
Locally Advanced Disease	76 (63%)
Rising PSA After Definitive Therapy	34 (28%)
Median PSA (25-75)	20.1 ng/dL (5.8-59.2)
Prior Therapy	
Surgery	57 (47.5%)
Radiation Therapy	20 (16.7%)
Hormonal Therapy	27 (22.5%)

¹This table is derived from the primary review.

Note that only 8% of patients had metastatic disease while 23 patients had a normal PSA (primarily patients with locally advanced disease) at study entry. While these findings should not affect the co-primary endpoints, it is clear that the study was not conducted in the indicated population.

Primary Endpoint

The study was designed with two co-primary endpoints:

- The percentage of patients achieving castrate levels of testosterone at Day 29; and
- The percentage maintaining castrate levels of testosterone from Day 57 to Day 337.

The protocol planned to perform an exact binomial estimate at Day 29 and to use a survival analysis to estimate the percentage of patients maintaining castrate testosterone levels from Day 57 to Day 337. The original protocol and the statistical analysis plan stated that the primary analysis would be performed on both the ITT and per protocol population (primary population unknown). The handling of missing data is as follows.

- In patients escaping castration level at a certain visit, subsequent missing data is irrelevant.
- Patients maintaining castration level up to a certain visit with missing data afterwards (drop out due to non-drug related reasons) will be excluded from the analysis.
- Patients maintaining castration level up to a certain visit with missing data afterwards (dropout due to drug related reasons) will be treated as having escaped the castration level (failure).
- Missing data between 2 visits where castration levels were maintained will be handled as missing for that particular visit, and considered as maintaining the castration level.
- Two consecutive missing data points between two visits where castration levels were maintained will be handled as missing and the patient will be considered as having escaped the castration level at those visits.

The applicant used two assay methods to assess testosterone levels. The table below presents the number of patients achieving castrate testosterone levels on Day 29 using the results of the (b) (4) immunoassay and the (b) (4) LC/MS assay. The protocol pre-defined a castrate testosterone level as < 1.735 nM.

Day 29

Testosterone Levels on Day 29	
Testosterone	Triptorelin 22.5 mg N = 120
Percent with Testosterone Levels \leq 1.735 nM (50 ng/dL)	
LC/MS Assay	117/120 (97.5%)
Immunoassay	112/120 (93.3%)

Using the LC/MS assay (which the applicant considers primary), 3 patients did not achieve castrate levels at Day 29. This includes two patients (02601, 03606) who did not have castrate levels on Day 29, but had castrate levels at the next assessment (Day 57) and all subsequent assessments. It also includes patient 11613 who did not achieve castrate levels until the second injection on Day 197.

Day 57-337

The tables below presents the number of patients maintaining castrate testosterone levels from Day 57 to Day 337. This uses both a Kaplan-Meier method, as specified in the original study protocol and an exact binomial method, as specified in the Statistical Analysis Plan.

Maintenance of Castrate Testosterone Levels Day 57 to 337		
Kaplan-Meier Estimate	Triptorelin 22.5 mg ITT, N = 120	Triptorelin 22.5 mg PP, N = 115
LC/MS Method (95% CI)	93.3% (88.7%; 97.8%)	93.0% (88.3%; 97.7%)
Immunoassay (95% CI)	91.6% (84.9%; 95.4%)	97.4% (94.5%; 100%)
Binomial Estimate	Triptorelin 22.5 mg N = 115	Triptorelin 22.5 mg PP, N = 110
LC/MS Method (95% CI)	93.0% (86.8%; 97.0%)	92.7% (86.2%; 96.8%)
Binomial Estimate	Triptorelin 22.5 mg N = 116	Triptorelin 22.5 mg PP, N = 111
Immunoassay (95% CI)	80.2% (72.0%; 87.0%)	79.3% (71.0%; 86.0%)

Using the LC/MS assay and the K-M estimate, 93.3% of the ITT population maintained a castrate testosterone level from Day 57 to 337. That is, 8 patients did not maintain a castrate testosterone level. FDA agrees with this analysis.

Using the LC/MS assay and the binomial estimate, 93.0% of the ITT population maintained a castrate testosterone level from Day 57 to 337. Using the applicant’s method which excludes 5 patients who did not complete the study (N = 115), 8 patients did not maintain a castrate testosterone level.

The table below provides exact binomial estimates using a variety of imputation methods and the results of the LC/MS assay. In these sensitivity assays, using the binomial method, the percentage of patients castrate from Days 57 to 337 ranged from 89.2% to 95.8%.

Sensitivity Analyses: Maintenance of Testosterone Levels Day 57 to Day 337				
Binomial Estimate	S1 N = 120	S2 N = 115	S3 N = 120	S4 N = 120
LC/MS	112/120 (93.3%)	107/115 (93.0%)	115/120 (95.8%)	107/120 (89.2%)

Finally, testosterone levels, using both the immunoassay and the LC/MS methods, are shown below. The first portion of the table shows the patients whose testosterone levels were elevated using the LC/MS method. In all but 2 cases, the testosterone level is also elevated using the immunoassay. The table includes only monthly testosterone levels and does not include the additional levels drawn in patients who participated in the pharmacokinetics studies.

The second portion of the table shows the patients whose testosterone levels were only elevated using the immunoassay. Note that patient 11611 participated in the pharmacokinetics studies and had a castrate testosterone level on Day 169, but an elevated level on Day 171. While the patients in this portion on the table only had elevated levels using 1 of the 2 assay methods, elevations tended to cluster at Day 169 and Day 337.

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Testosterone Levels Using the (b) (4) Immunoassay and the (b) (4) Liquid Chromatography/Mass Spectroscopy Methods																										
Patient #	Day 1		Day 29		Day 57		Day 85		Day 113		Day 141		Day 169		Day 197		Day 225		Day 253		Day 281		Day 309		Day 337	
	I ¹	MS ¹	I	MS	I	MS	I	MS	I	MS	I	MS	I	MS	I	MS	I	MS	I	MS	I	MS	I	MS	I	MS
Elevated by the (b) (4) Method (LC/MS)																										
04602	26.19	22.423	1.76	1.19	1.38	.624	1.49	.841	1.63	.663	1.42	.546	2.08	.374	1.73	.902	1.76	.797	1.49	.656	1.04	.769	1.8	.836	41.8	42.047
06604	11.8	13.112	1.28	.774	.69	.398	.83	.339	.87	.385		.393	1.49	1.938	.66	.176	.76	.219	.66	.338	.83	.471	.97	.338	.97	.382
06608	13.42	14.195	1.11	.668	.45	.333	.8	.451	4.5	6.119	.52	.252	1.04	.373	.8	.456	1.07	.272	.62	.442	.69	.724	.76	.275	1.11	.388
08604	15.5	18.867	.97	.828	.87	.611	1.21	.59	1	.365	.59	.307	1.63	.753	.66	.377	.62	.613	1.14	.49	.8	.664	1.31	.683	1.25	.801
10601	18.44	18.446	.87	.559		.233		.295	.76	.256	.73		.9	.282	.66	.201	1.14	.61	3.46	5.201	8.48	8.98	8.82	8.311	13.22	11.436
11606	11.56	18.522	1.63	1.30	2.77	2.333	.83	.447	1.45	.756	1	.316	1.76	.551	1.04	.629	1.35	.699	1.38	.658	1.07	.894	1.73	.652	1.73	1.077
11613	22.21	17.545	12.77	14.6	15.5		13.74	6.745	14.53	11.028	12.978	7.091	14.22	7.242	1.8	.763	2.25	.862	1.8	.55	1.9	.984	1.7	.649	1.94	.679
13613	27.26	27.553	1.73	1.11	1.25	.706	1.35	.46	3.25	3.354	1	.469	1.31	.648	.93	.522	1.73	.653	1.11	.463	1.59	1.553	.59	.486	1.63	.792
Elevated by the (b) (4) Method (Immunoassay)																										
01604	16.71	16.811	1.18	.77	.93	.352	1.11	.464	1.35	.998	1.59	.347	1.11	.464	1.59	.493	1.31	.262	1.49	.621	.66	.349	1.38	.886	1.76	.415
05606	9.58	7.978	2.53	.739	2.32	.614	2.04	.573	2.08	.874	2.35	.801	1.87	.233	1.66	.46	1.49	.338	2.01	.589	1.52	.442	1.94	1.245	1	.244
08602	9.24	13.86	.9	.484	1	.512	1.56	.576	1.11	.61	1.04	.245	1.49	.503	.52	.283	1.35	.504	1.7	.487	1.42	.83	1.94	.377	1.59	.685
08605	24.6	25.852	2.46	1.22	1.35	.558	1.56	.416	1.11	.536	1.7	.208	3.18	1.33	.83	.169	1.38	.554	1.49	.752	2.01	1.347	.87	.658	1.66	.602
10603	16.68	15.739	1.14	.557	1.14	.312	1.31	.292	1	.209	1.25	.228	1.25	.392	1	.195	1.13	.387	.83	.513	.69	.167	2.11	.315	1.28	.271
11609	13.74	17.412	1.28	.543	.8	.341	.8	.304	.76	.345	1.14	.214	1.76	.354	.83	.293	1.11	.299	.97	.202	1.04	.602	1.18	.298	.8	.526
11611	27.61	22.481	.8	.892	.55	.284	1.11	.435	1.07	.892	.59	.226	.76	.393	.83	.394	.93	.262	.73	.429	.8	.433	.62	.377	1.18	.527
11614	19.65	16.305	1.49	.568	1.21	.456	1.52	.417	1.35	.586	1.04	.22	1.76	.391	1.31	.392	1.52	.268	1	.289	.97	.539	.87	.582	1.35	.64
12603	17.51	16.34	1.28	.671	1.28	.748	1.56	.689	1.63	1.029	2.84	.674	1.8	.791	2.25	.845	2.25	.945	1.66	1.075	1.66	.952	1.87	1.414	2.15	.875
13601	20.03	25.369	1.52	.97	1.49	.666	.73	.46	1.45	.48	1.28	.646	1.94	.512	1.21	.616	.8	.446	1.73	.575	1.42	.762	1.56	.67	1.56	.505
13602	11.63	14.418	1.45	.75	1.11	.479	.69	.477	1.28	.67	.8	.456	1.8	.683	.97	.383	1.04	.916	1.11	.441	.66	.818	1.42	.663	.83	.698
13609	12.39	20.382	1.63	.855	1	.437	1.11	.186	1.45	.624	1.42	.751	1.87	.396	.69	.336	1.18	.511	1.31	.429	1.45	1.059	1.25	.426	1.11	.66
13612	16.57	20.484	1.21	.498	1.21	.559	1.18	.439	1.25	.722	1.87	.414	1.7	.391	1.14	.577	1.25	.485	1.38	.501	1.25	.726	1.63	.257	1.7	.499
13616	15.78	16.539	1.66	.875	.73	.344	1.31	.239	1.28	.585	1.63	.447	1.56	.726	1.18	.712	.76	.489	1.42	.998	1.76	1.34	1.11	1.118	1.59	.734
13618	17.92	19.017	1.49	.705	1.31	.464	1.31	.421	1.28	.305	1.45	.305	1.56	.401	.8	.286	.87	.276	1.45	.504	1.8	1.074	1.35	.331	1.35	.436

¹I-Immunoassay; MS-Liquid Chromatography Tandem Mass Spectroscopy

Secondary Endpoints

The findings above should be considered in terms of the effect non-castrate testosterone levels on the underlying disease. However, the only estimate of disease burden recorded by the applicant was the PSA. The 2 patients who discontinued due to progressive disease, but with castrate testosterone levels using the LC/MS assay had an elevated PSA prior to discontinuation. Among the 8 patients with non-castrate testosterone levels from Day 57 to Day 337 using the LC/MS assay, 2 had an elevated PSA (04602, 10601) and an elevated testosterone at Day 337.

Conclusion

Using the LC/MS assay, the co-primary endpoints are in the range of previous approvals for GnRH agonists. However, using the results of the immunoassay, the co-primary endpoints are well below the range of previous approvals for GnRH agonists. The LC/MS assay is better able to detect hypogonadal testosterone levels and similar methods have been used for previous approvals. The applicant should be asked to address the use of the two different assays and to provide a compelling rationale for the use of the LC/MS results (as used in their final study report).

8. Safety

The triptorelin 22.5 mg safety database includes only 128 patients. One hundred and twenty patients were treated on DEB-TRI6M-301. Eight patients on DEB-TRI6M-201 received the formulation taken forward into study 301. The analyses below focus on the 120 patients treated under DEB-TRI6M-301. While this database is small, the adverse events seen with triptorelin 22.5 mg are consistent with those seen with the 4 week (3.75 mg) and 12 week (11.25 mg) formulations and no new safety signals were seen. This database was, therefore, considered acceptable.

Deaths

There were 3 deaths on study. Patient 11615 died on Day 85 due to a cardiac arrest. He had an extensive history of cardiovascular disease and castrate testosterone levels at the time of his death.

Patients 05612 and 05614 are very similar. Both had newly diagnosed prostate cancer and both died of progressive disease 8 and 9 months after diagnosis. Their short course is unusual. Both patients were diagnosed with T3NXMX disease in June 2006 and underwent radical prostatectomy. Both entered the study in August 2006. At the time of entry, both had markedly elevated PSAs (684 µg/L-05612, 446 µg/L-05614). This suggests that both patients had widely metastatic disease at the time of entry. Both attained castrate testosterone levels that were initially accompanied by a decrease in PSA. However, both presented on

approximately Day 169 with an increase in bone pain, castrate testosterone levels, and a rising PSA. Both died at their homes.

No adverse events led to discontinuation.

Serious Adverse Events

Fourteen patients had a serious adverse event on study. Serious adverse events related to the patient’s prostate cancer and to their response to triptorelin 22.5 mg include hematuria (1), obstructive uropathy (1), and bone metastases/metastatic prostate cancer (2).

- Patient 03606 had obstructive uropathy at the time of study entry. He did not achieve castrate testosterone levels until Day 57 and required a TURP for the treatment of obstruction.
- Patient 11605 developed hematuria after replacement of his supra-pubic catheter.
- Patient 08609 developed worsening pain despite castrate testosterone levels and underwent a bilateral orchiectomy and radiation therapy.
- Patient 11621 had castrate testosterone levels but developed bone pain and a worsening bone scan.

Adverse Events

Grade 3 Adverse Events

Events were graded as mild, moderate, or severe by the investigator. Twenty-four grade 3 events were reported in 17 patients. These are listed in the table below. These events are consistent with the known effect on androgen deprivation therapy as well as the general condition of elderly patients with prostate cancer.

Grade 3 Adverse Events	
Adverse Event	Triptorelin 22.5 mg N = 120
Cardiac Disorders	
Myocardial Infarction	2
Atrial Flutter	1
Infections	
Herpes Zoster	1
Pneumonia	1
Injury, Poisoning and Procedural Complications	
Soft Tissue Injury	1
Metabolism and Nutrition Disorders	
Anorexia	1
Dehydration	1
Musculo-Skeletal and Connective Tissue Disorders	
Arthritis	1
Back Pain	1

Grade 3 Adverse Events	
Adverse Event	Triptorelin 22.5 mg N = 120
Bone Pain	1
Neoplasms	
Prostate Cancer	3
Metastases to Bone	2
Penis Carcinoma	1
Nervous System Disorders	
Diabetic Neuropathy	1
Psychiatric Disorders	
Loss of Libido	1
Renal and Urinary Disorders	
Obstructive Uropathy	1
Urinary Retention	1
Reproductive System and Breast Disorders	
Erectile Dysfunction	1
Vascular Disorders	
Hot Flush	1

All Adverse Events

Grade 1-4 adverse events which occurred in $\geq 10\%$ of patients are shown below. These events are consistent with the known effects of androgen deprivation therapy. Further information on elevated transaminases is included under the analysis of laboratory events below.

Adverse Events in $\geq 10\%$ of Patients ¹	
Adverse Reaction	Triptorelin 22.5 mg N = 120
Hot Flush	87 (72.5%)
Weight Gain	41 (36.3%)
Increase in Hepatic Transaminase	23 (19.2%)
Influenza	20 (16.0%)
Hypertension	17 (14.2%)
Back pain	13 (10.8%)
Erectile Dysfunction	12 (10.0%)
Urinary Tract Infection	11 (10.0%)

¹Derived from the primary review

Local Reactions

Patients were seen on the day of injection and observed for 4 hours after each injection. During the 4 hour observation period redness (1 patient), local pain (4), swelling (4), bruising (2) and induration (2) were reported.

Patients were next seen 28 days after injection. Examining adverse events over the entire reporting period, the following injection site reactions were reported; bruising (2 patients), erythema (1), induration (2), pain (2), pruritus (1), and swelling (1). The gap between injection and the next study visit may have resulted in under reporting of local reactions.

Laboratories

A CBC and chemistries were obtained at baseline, the day of injection, and at the last study visit. The laboratory values were graded by the primary reviewer using the NCI CTCAE v 3.0 and the values in the table include all laboratories with a grade shift on study. Although an increase in hepatic transaminases is listed as a common adverse event, only one patient had a documented grade 2 ALT. This value later returned to baseline.

On Study Laboratories with a Grade Shift ¹				
Laboratory (%)	Triptorelin 22.5 mg N=120			
	All Grades	Grade 1/2	Grade 3	Grade 4
Increase in ALT/AST	23 (19%)	23* (19%)	0	0
Decrease in Hemoglobin	25 (21%)	23 (19%)	2 (2%)	0
Hyperglycemia	30 (25%)	27 (23%)	3 (3%)	0
Increase in Creatinine	11 (9%)	11 (9%)	0	0

¹Derived from the primary review

Post-Marketing Safety Reports

The applicant provided an update on the adverse events voluntarily submitted for the approved product. These events are difficult to interpret since the reporting requirements are not specified and since the number of treated patients is unknown. Anaphylaxis was reported in 3 patients receiving triptorelin. This will be included in the product label.

9. Advisory Committee Meeting

An Advisory Committee meeting will not be held to discuss the 24 week formulation of triptorelin pamoate 22.5 mg. A large number of GnRH agonists and antagonists have been previously approved and the standards set for their approval.

10. Pediatrics

A pediatric waiver was granted for this indication, advanced prostate cancer.

11. Other Relevant Regulatory Issues

No irregularities were found during the clinical inspections of two sites in South Africa. The financial disclosures were evaluated by the primary reviewer and found acceptable.

12. Labeling

Please see final package insert and carton and container labels. Labeling for 3 formulations of Triptorelin pamoate, 3.75 mg, 11.25 mg, and 22.5 mg, was consolidated into one package insert.

13. Recommendations/Risk Benefit Assessment

- Recommendation

Both CMC and clinical deficiencies were identified during the initial review and a complete response letter was sent asking the applicant to address these issues.

- 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 patients with prostate cancer. Grade 1-4 adverse events in $\geq 10\%$ of patients include hot flush, weight gain, increase in hepatic transaminases, influenza, hypertension, back pain, erectile dysfunction, and urinary tract infection.
 - Using the analyses specified in the Statistical Analysis Plan and testosterone levels obtained by the LC/MS method, castrate testosterone levels were achieved in 97.5% (92.9%; 99.5%) of patients at Day 29. From Day 57-337, 93.0% (86.8%; 97.0%) of patients maintained castrate testosterone levels.
 - Using testosterone levels obtained by the immunoassay method, these results were much lower.
- Recommendation for Postmarketing Risk Management Activities

No postmarketing risk management activities are recommended.

- Recommendation for other Postmarketing Study Commitments

No post-marketing commitments or requirements are recommended.

- Recommended Comments to Applicant

ADDENDUM

On July 10, 2009, the FDA issued a complete response letter asking the applicant to address several product quality issues and one clinical concern. On September 10, 2009, the applicant provided a Class 2 resubmission addressing these issues.

Chemistry

That applicant addressed 13 comments concerning product manufacturing in the complete response letter. These concerns involved drug master files, drug substance, drug product, and the inspection of manufacturing sites. All chemistry concerns were addressed, including master file deficiencies (please see CMC review). Sites of product manufacturing and control were inspected. However, at the time of this review the inspection report for 1 site is pending. An addendum will be written to this report when that inspection is complete.

Clinical

- 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 [REDACTED] (b) (4) [REDACTED] were lower than those by obtained by immunoassay in [REDACTED] (b) (4) [REDACTED], 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 ± 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.

CONCLUSION

Watson Laboratories has adequately addressed the issues raised in the complete response letter and I recommend approval of Trelstar 22.5 mg.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22437

ORIG-1

WATSON
LABORATORIES
INC

TRELSTAR (b) (4)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

VIRGINIA E MAHER
03/05/2010