

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***

**NDA 21343/ S33**

***Trade Name:***      **ELIGARD**

***Generic Name:***    Leuprolide Acetate

***Sponsor:***          **Tolmar Pharmaceuticals, Inc.**

***Approval Date:***    02/29/2016

***Indications:***      ELIGARD® is a gonadatropin releasing hormone (GnRH) agonist indicated for the palliative treatment of advanced prostate cancer.

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*  
**NDA 21343/S33**

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**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*  
**NDA 21343/S33**

**APPROVAL LETTER**



NDA 021343/S-033  
NDA 021379/S-033  
NDA 021488/S-030  
NDA 021731/S-029

## SUPPLEMENT APPROVAL

TOLMAR Therapeutics, Inc.  
Attention: Michelle R. Ryder  
Vice President, Regulatory Affairs  
701 Centre Avenue  
Fort Collins, CO 80526

Dear Ms. Ryder:

Please refer to your Supplemental New Drug Applications (sNDAs) dated September 23, 2015, received September 23, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Eligard<sup>®</sup> (leuprolide acetate for injectable solution) 7.5 mg, 22.5 mg, 30 mg, and 45 mg.

These "Prior Approval" supplemental new drug applications propose the following changes:

1. Revisions to the label to add room temperature storage information in Section 2 (Dosage and Administration) and in subsection 16.2 (Storage) to allow for flexibility when prescribing, preparing and administering the product to the patient.
2. Editorial revisions throughout the package insert for clarity.

### **APPROVAL & LABELING**

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

### **CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling. Information on

NDA 021343/S-033  
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submitting SPL files using eList may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

### **REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

### **REPORTING REQUIREMENTS**

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Rajesh Venugopal, Senior Regulatory Project Manager, at (301) 796-4730.

Sincerely,  
*{See appended electronic signature page}*

Geoffrey Kim, MD  
Director  
Division of Oncology Products 1  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

ENCLOSURE(S):  
Content of Labeling

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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GEOFFREY S KIM  
02/29/2016

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 21343/S33**

**LABELING**

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ELIGARD® safely and effectively. See full prescribing information for ELIGARD®.

**ELIGARD® (leuprolide acetate for injectable suspension)**

**Initial U.S. Approval: 2002**

### RECENT MAJOR CHANGES

Dosage and Administration (2)	10/2014
Warnings and Precautions (5.5)	10/2014

### INDICATIONS AND USAGE

ELIGARD® is a gonadotropin releasing hormone (GnRH) agonist indicated for the palliative treatment of advanced prostate cancer (1)

### DOSAGE AND ADMINISTRATION

- 7.5 mg subcutaneously every month (2)
- 22.5 mg subcutaneously every 3 months (2)
- 30 mg subcutaneously every 4 months (2)
- 45 mg subcutaneously every 6 months (2)

### DOSAGE FORMS AND STRENGTHS

- Injectable suspension: 7.5 mg (3)
- Injectable suspension: 22.5 mg (3)
- Injectable suspension: 30 mg (3)
- Injectable suspension: 45 mg (3)

### CONTRAINDICATIONS

- Known hypersensitivity to GnRH, GnRH agonist analogs or any of the components of ELIGARD® (4.1)
- Pregnancy (4.2)

### WARNINGS AND PRECAUTIONS

- Tumor Flare; Transient increase in serum levels of testosterone during treatment may result in worsening of symptoms or onset of new signs and symptoms during the first few weeks of treatment, including bone pain, neuropathy, hematuria, bladder outlet obstruction, ureteral obstruction, or spinal cord compression. Monitor patients at risk closely and manage as appropriate (5.1, 5.2)
- Hyperglycemia and diabetes: Hyperglycemia and an increased risk of developing diabetes have been reported in men receiving GnRH analogs. Monitor blood glucose level and manage according to current clinical practice. (5.3)
- Cardiovascular diseases: Increased risk of myocardial infarction, sudden cardiac death and stroke has been reported in men. Monitor for cardiovascular disease and manage according to current clinical practice (5.4)
- Effect on QT/QTc Interval: Androgen deprivation therapy may prolong the QT interval. Consider risks and benefits. (5.5)

### ADVERSE REACTIONS

- Most common adverse reactions in clinical studies (incidence  $\geq 5\%$ ): Malaise, fatigue, hot flashes/sweats, and testicular atrophy. (6.1)
- As with other GnRH agonist, other adverse reactions, including decreased bone density and rare cases of pituitary apoplexy have been reported (6.1, 6.2)

To report SUSPECTED ADVERSE REACTIONS, contact TOLMAR Pharmaceuticals, Inc. at 1-888-354-4273 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### USE IN SPECIFIC POPULATIONS

- Pregnancy: ELIGARD® should not be used in pregnancy (8.1)
- Safety and effectiveness in pediatric patients have not been established (8.4)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 02/2016

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## FULL PRESCRIBING INFORMATION

### 1. INDICATIONS AND USAGE

ELIGARD<sup>®</sup> is indicated for the palliative treatment of advanced prostate cancer.

### 2. DOSAGE AND ADMINISTRATION

As with other similar agents, the use of gloves is recommended during mixing and administration.<sup>1</sup>

ELIGARD<sup>®</sup> is administered **subcutaneously** and provides continuous release of leuprolide acetate over a one-, three-, four-, or six-month treatment period (Table 1). The injection delivers the dose of leuprolide acetate incorporated in a polymer formulation.

**Table 1. ELIGARD<sup>®</sup> Recommended Dosing**

Dosage	7.5 mg	22.5 mg	30 mg	45 mg
Recommended dose	1 injection every month	1 injection every 3 months	1 injection every 4 months	1 injection every 6 months

As with other drugs administered by subcutaneous injection, the injection site should vary periodically. The specific injection location chosen should be an area with sufficient soft or loose subcutaneous tissue. In clinical trials, the injection was administered in the upper- or mid-abdominal area. Avoid areas with brawny or fibrous subcutaneous tissue or locations that could be rubbed or compressed (i.e., with a belt or clothing waistband).

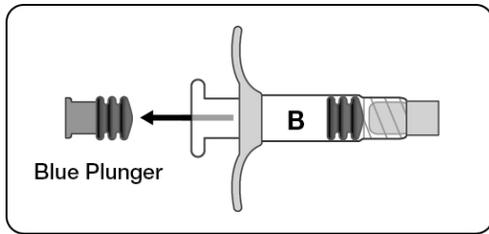
#### 2.1 Mixing Procedure

**IMPORTANT: Allow the product to reach room temperature before mixing. Once mixed, the product must be administered within 30 minutes or it should be discarded.**

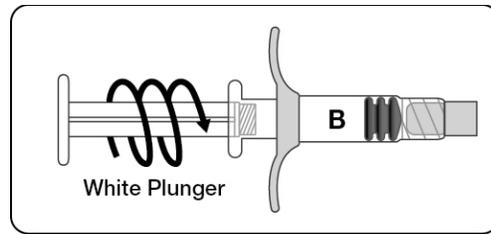
Follow the detailed instructions below to ensure proper preparation of ELIGARD<sup>®</sup> prior to administration:

ELIGARD<sup>®</sup> is packaged in two thermoformed trays. Each carton contains:

- One sterile syringe (Syringe A) pre-filled with the ATRIGEL<sup>®</sup> Delivery System
  - One sterile syringe (Syringe B) pre-filled with leuprolide acetate powder
  - One long white plunger rod for use with Syringe B
  - One sterile needle or One sterile safety needle
  - Desiccant pack(s)
1. On a clean field, open all of the packages and remove the contents. Discard the desiccant pack(s).

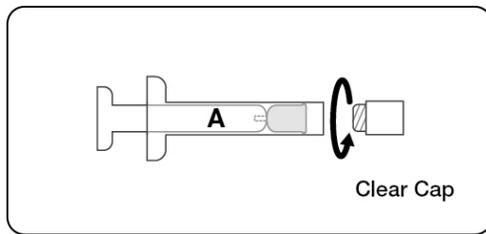


**Figure 1**

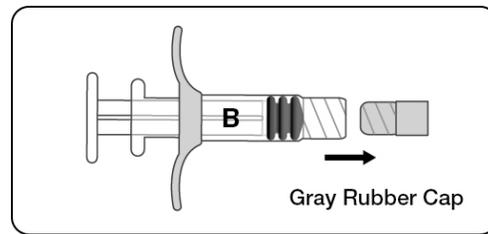


**Figure 2**

2. **Pull out the short blue plunger rod with attached grey stopper from Syringe B and discard (Figure 1).** Twist the long, white replacement plunger rod into the gray primary stopper remaining in Syringe B (Figure 2).

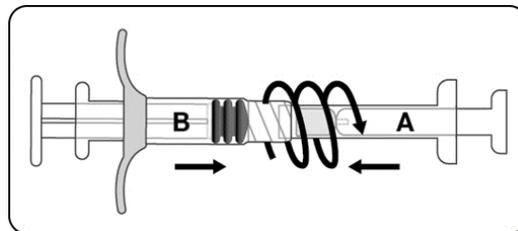


**Figure 3**



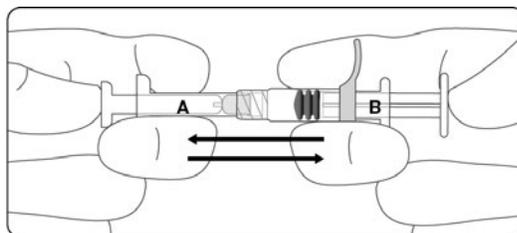
**Figure 4**

3. Unscrew and discard the clear cap from Syringe A (Figure 3). **Remove and discard the gray rubber cap from Syringe B (Figure 4).**



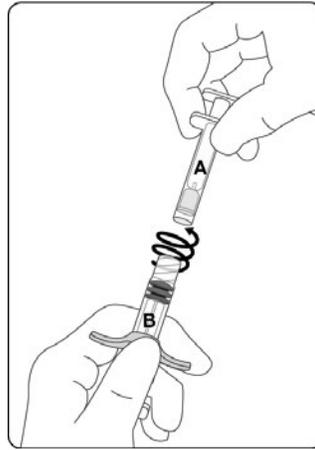
**Figure 5**

4. Join the two syringes together by pushing and twisting until secure (Figure 5).



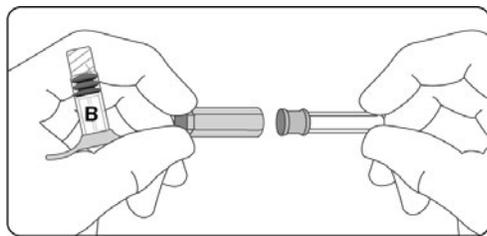
**Figure 6**

5. Inject the liquid contents of Syringe A into Syringe B that contains the leuprolide acetate powder. Thoroughly mix the product for approximately 45 seconds by pushing the contents back and forth between both syringes to obtain a uniform suspension (Figure 6). When thoroughly mixed, the suspension will appear light tan to tan (ELIGARD<sup>®</sup> 7.5 mg) or colorless to pale yellow (ELIGARD<sup>®</sup> 22.5 mg, 30 mg and 45 mg). **Please Note: Product must be mixed as described; shaking will NOT provide adequate mixing of the product.**

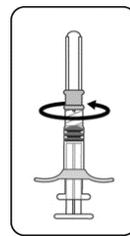


**Figure 7**

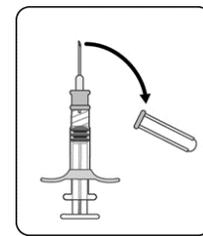
6. After mixing, hold the syringes vertically with Syringe B on the bottom. The syringes should remain securely coupled. Draw the entire mixed product into Syringe B (short, wide syringe) by depressing the Syringe A plunger and slightly withdrawing the Syringe B plunger. Unscrew Syringe A to decouple the syringes while continuing to push down on the Syringe A plunger (Figure 7). **Note: Small air bubbles will remain in the formulation – this is acceptable.**



**Figure 8**



**Figure 9**

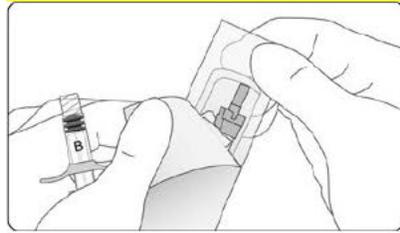


**Figure 10**

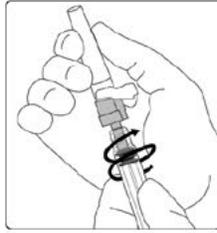
*[Applies to ELIGARD<sup>®</sup> single use kit of a two syringe-mixing system with **sterile needle**]*

7. Hold Syringe B vertically. Remove and discard the cap on the bottom of the sterile needle cartridge by twisting it (Figure 8). Attach the needle cartridge to the end of

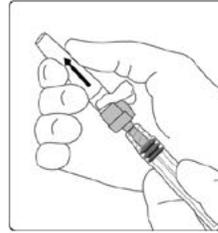
Syringe B (Figure 9) by pushing in and turning the needle until it is firmly seated. Do not overtwist the needle onto the syringe because the thread may become stripped. Pull off the clear needle cartridge cover prior to administration (Figure 10).



**Figure 11**



**Figure 12**



**Figure 13**

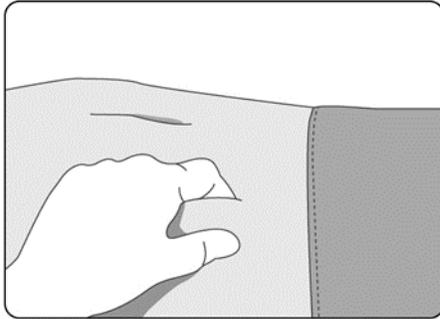
*[Applies to ELIGARD® single use kit of a two syringe-mixing system with sterile safety needle]*

8. Hold Syringe B vertically. Open the sterile safety needle package by peeling back the paper tab and remove the safety needle (Figure 11). Secure the needle to the end of Syringe B by holding the protective needle sheath and twisting the syringe clockwise to fully seat the needle (Figure 12). Do not overtwist the needle onto the syringe because the thread may become stripped. Remove the protective needle sheath prior to administration (Figure 13).

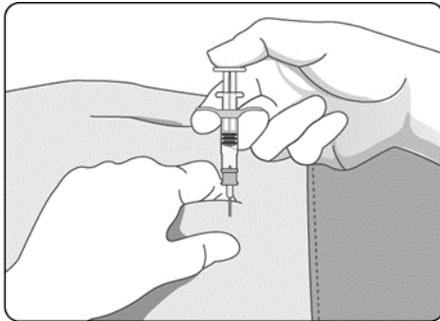
## 2.2 Administration Procedure

**IMPORTANT: Allow the product to reach room temperature before mixing. Once mixed, the product must be administered within 30 minutes or it should be discarded.**

1. Choose an injection site on the abdomen, upper buttocks, or another location with adequate amounts of subcutaneous tissue that does not have excessive pigment, nodules, lesions, or hair. Since you can vary the injection site for **subcutaneous** injections, choose an area that hasn't recently been used.
2. Cleanse the injection-site area with an alcohol swab.

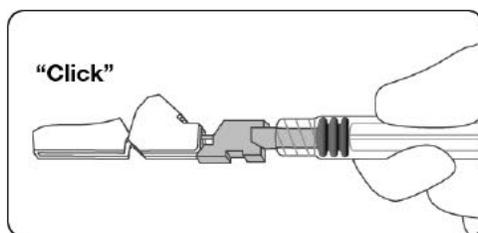
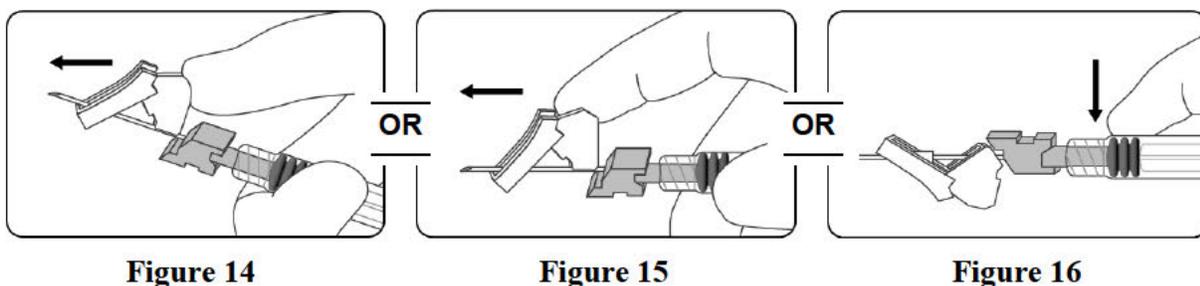


3. Using the thumb and forefinger of your non-dominant hand, grab and bunch the area of skin around the injection site.



4. Using your dominant hand, insert the needle quickly at a 90° angle to the skin surface. The depth of penetration will depend on the amount and fullness of the subcutaneous tissue and the length of the needle. After the needle is inserted, release the skin with your nondominant hand.

5. Inject the drug using a slow, steady push. Press down on the plunger until the syringe is empty.
6. Withdraw the needle quickly at the same 90° angle used for insertion.



[Step 7 only applies to ELIGARD<sup>®</sup> single use kit of a two syringe-mixing system with *sterile safety needle*]

7. Immediately following the withdrawal of the needle, activate the safety shield on the needle by using a thumb (Figure 14) or finger (Figure 15) or a flat surface (Figure 16) to push the safety shield forward until it completely covers the needle tip and locks into place. An audible and tactile “click” verifies a locked position for the safety shield (Figure 17).
8. Discard all components safely in an appropriate biohazard container.

### 3. DOSAGE FORMS AND STRENGTHS

ELIGARD<sup>®</sup> is an injectable suspension of leuprolide acetate available in a single use kit. The kit consists of a two-syringe mixing system, a sterile needle or a sterile safety needle (Table 2), a silica gel desiccant pouch to control moisture uptake, and a package insert for constitution and administration procedures. Each syringe is individually packaged. One contains the ATRIGEL<sup>®</sup> Delivery System and the other contains leuprolide acetate powder. When constituted, ELIGARD<sup>®</sup> is administered as a single dose.

**Table 2. ELIGARD<sup>®</sup> Needle specifications**

ELIGARD <sup>®</sup> formulation	Sterile needle		Sterile safety needle	
	Gauge	Length	Gauge	Length
7.5 mg	20-gauge	1/2-inch	20-gauge	5/8-inch
22.5 mg	20-gauge	1/2-inch	20-gauge	5/8-inch
30 mg	20-gauge	5/8-inch	20-gauge	5/8-inch
45 mg	18-gauge	5/8-inch	18-gauge	5/8-inch

## 4. CONTRAINDICATIONS

### 4.1 Hypersensitivity

ELIGARD<sup>®</sup> is contraindicated in patients with hypersensitivity to GnRH, GnRH agonist analogs or any of the components of ELIGARD<sup>®</sup>. Anaphylactic reactions to synthetic GnRH or GnRH agonist analogs have been reported in the literature.

### 4.2. Pregnancy

ELIGARD<sup>®</sup> may cause fetal harm when administered to a pregnant woman. Expected hormonal changes that occur with ELIGARD<sup>®</sup> treatment increase the risk for pregnancy loss and fetal harm when administered to a pregnant woman [*see Use in Specific Populations (8.1)*]. ELIGARD<sup>®</sup> is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to the fetus.

## 5. WARNINGS AND PRECAUTIONS

### 5.1 Tumor Flare

ELIGARD<sup>®</sup> 7.5 mg 22.5 mg 30 mg, like other GnRH agonists, causes a transient increase in serum concentrations of testosterone during the first week of treatment. ELIGARD<sup>®</sup> 45 mg causes a transient increase in serum concentrations of testosterone during the first two weeks of treatment. Patients may experience worsening of symptoms or onset of new signs and symptoms during the first few weeks of treatment, including bone pain, neuropathy, hematuria, or bladder outlet obstruction.

Cases of ureteral obstruction and/or spinal cord compression, which may contribute to paralysis with or without fatal complications, have been observed in the palliative treatment of advanced prostate cancer using GnRH agonists.

Patients with metastatic vertebral lesions and/or with urinary tract obstruction should be closely observed during the first few weeks of therapy. If spinal cord compression or ureteral obstruction develops, standard treatment of these complications should be instituted.

### 5.2 Laboratory Tests

Response to ELIGARD<sup>®</sup> should be monitored by periodic measurement of serum concentrations of testosterone and prostate specific antigen.

In the majority of patients, testosterone levels increased above Baseline during the first week, declining thereafter to Baseline levels or below by the end of the second or third week. Castrate levels were generally reached within two to four weeks.

Castrate testosterone levels were maintained for the duration of the treatment with ELIGARD<sup>®</sup> 7.5 mg. No increases to above the castrate level occurred in any of the patients.

Castrate levels were generally maintained for the duration of treatment with ELIGARD<sup>®</sup> 22.5 mg.

Once castrate levels were achieved with ELIGARD<sup>®</sup> 30 mg, most (86/89) patients remained suppressed throughout the study.

Once castrate levels were achieved with ELIGARD<sup>®</sup> 45 mg, only one patient (< 1%) experienced a breakthrough, with testosterone levels > 50 ng/dL.

Results of testosterone determinations are dependent on assay methodology. It is advisable to be aware of the type and precision of the assay methodology to make appropriate clinical and therapeutic decisions.

*Drug/Laboratory Test Interactions:* Therapy with leuprolide acetate results in suppression of the pituitary-gonadal system. Results of diagnostic tests of pituitary gonadotropic and gonadal functions conducted during and after leuprolide therapy may be affected.

### **5.3 Hyperglycemia and Diabetes**

Hyperglycemia and an increased risk of developing diabetes have been reported in men receiving GnRH agonists. Hyperglycemia may represent development of diabetes mellitus or worsening of glycemic control in patients with diabetes. Monitor blood glucose and/or glycosylated hemoglobin (HbA1c) periodically in patients receiving a GnRH agonist and manage with current practice for treatment of hyperglycemia or diabetes.

### **5.4 Cardiovascular Diseases**

Increased risk of developing myocardial infarction, sudden cardiac death and stroke has been reported in association with use of GnRH agonists in men. The risk appears low based on the reported odds ratios, and should be evaluated carefully along with cardiovascular risk factors when determining a treatment for patients with prostate cancer. Patients receiving a GnRH agonist should be monitored for symptoms and signs suggestive of development of cardiovascular disease and be managed according to current clinical practice.

### **5.5 Effect on QT/QTc Interval**

Androgen deprivation therapy may prolong the QT/QTc interval. Providers should consider whether the benefits of androgen deprivation therapy outweigh the potential risks in patients with congenital long QT syndrome, congestive heart failure, frequent electrolyte abnormalities, and in patients taking drugs known to prolong the QT interval. Electrolyte abnormalities should be corrected. Consider periodic monitoring of electrocardiograms and electrolytes.

## **6. ADVERSE REACTIONS**

### **6.1 Clinical trial experience**

The safety of all ELIGARD<sup>®</sup> formulations was evaluated in clinical trials involving patients with advanced prostate cancer. In addition, the safety of ELIGARD<sup>®</sup> 7.5 mg was evaluated in 8 surgically castrated males (Table 4). ELIGARD<sup>®</sup>, like other GnRH analogs, caused a transient increase in serum testosterone concentrations during the first one to two weeks of treatment. Therefore, potential exacerbations of signs and symptoms of the disease during the first weeks of treatment are of concern in patients with vertebral metastases and/or urinary obstruction or hematuria. If these conditions are aggravated, it may lead to neurological problems such as

weakness and/or paresthesia of the lower limbs or worsening of urinary symptoms [see *WARNINGS AND PRECAUTIONS (5.2)*].

During the clinical trials, injection sites were closely monitored. Refer to Table 3 for a summary of reported injection site events.

**Table 3. Reported Injection Site Adverse Events**

<b>ELIGARD®</b>	<b>7.5 mg</b>	<b>22.5 mg</b>	<b>30 mg</b>	<b>45 mg</b>
<b>Study number</b>	AGL9904	AGL9909	AGL0001	AGL0205
<b>Number of patients</b>	120	117	90	111
<b>Treatment</b>	1 injection every month up to 6 months	1 injection every 3 months up to 6 months	1 injection every 4 months up to 8 months	1 injection every 6 months up to 12 months
<b>Number of injections</b>	716	230	175	217
<b>Transient burning/stinging</b>	248 (34.6%) injections; 84% reported as mild	50 (21.7%) injections; 86% reported as mild	35 (20%) injections; 100% reported as mild	35 (16%) injections; 91.4% reported as mild <sup>3</sup>
<b>Pain (generally brief and mild)</b>	4.3% of injections (18.3% of patients)	3.5% of injections (6.0% of patients)	2.3% of injections <sup>2</sup> (3.3% of patients)	4.6% of injections <sup>4</sup>
<b>Erythema (generally brief and mild)</b>	2.6% of injections (12.5% of patients)	0.9% of injections <sup>1</sup> (1.7% of patients)	1.1% of injections (2.2% of patients)	
<b>Bruising (mild)</b>	2.5% of injections (11.7% of patients)	1.7% of injections (3.4% of patients)		2.3% of injections <sup>5</sup>
<b>Pruritus</b>	1.4% of injections (9.2% of patients)	0.4% of injections (0.9% of patients)		
<b>Induration</b>	0.4% of injections (2.5% of patients)			
<b>Ulceration</b>	0.1% of injections (> 0.8% of patients)			

1. Erythema was reported following 2 injections of ELIGARD® 22.5 mg. One report characterized the erythema as mild and it resolved within 7 days. The other report characterized the erythema as moderate and it resolved within 15 days. Neither patient experienced erythema at multiple injections.

2. A single event reported as moderate pain resolved within two minutes and all 3 mild pain events resolved within several days following injection of ELIGARD® 30 mg.

3. Following injection of ELIGARD® 30 mg, three of the 35 burning/stinging events were reported as moderate.

4. Transient pain was reported as mild in intensity in nine of ten (90%) events and moderate in intensity in one of ten (10%) events following injection of ELIGARD® 45 mg.

5. Mild bruising was reported following 5 (2.3%) study injections and moderate bruising was reported following 2 (<1%) study injections of ELIGARD® 45 mg.

These localized adverse events were non-recurrent over time. No patient discontinued therapy due to an injection site adverse event.

The following possibly or probably related systemic adverse events occurred during clinical trials with ELIGARD®, and were reported in > 2% of patients (Table 4). Often, causality is

difficult to assess in patients with metastatic prostate cancer. Reactions considered not drug-related are excluded.

**Table 4. Summary of Possible or Probably Related Systemic Adverse Events Reported by > 2% of Patients treated with ELIGARD®**

ELIGARD®		7.5 mg	7.5 mg	22.5 mg	30 mg	45 mg
<b>Study number</b>		AGL9904	AGL9802	AGL9909	AGL0001	AGL0205
<b>Number of patients</b>		120	8	117	90	111
<b>Treatment</b>		1 injection every month up to 6 months	1 injection (surgically castrated patients)	1 injection every 3 months up to 6 months	1 injection every 4 months up to 8 months	1 injection every 6 months up to 12 months
<b>Body system</b>	<b>Adverse event</b>	<b>Number (percent)</b>				
<b>Body as a whole</b>	Malaise and fatigue	21 (17.5%)		7 (6.0%)	12 (13.3%)	13 (11.7%)
	Weakness					4 (3.6%)
<b>Nervous system</b>	Dizziness	4 (3.3%)			4 (4.4%)	
<b>Vascular</b>	Hot flashes/sweats	68 (56.7%)*	2 (25.0%)*	66 (56.4%)*	66 (73.3%)*	64 (57.7%)*
<b>Renal/urinary</b>	Urinary frequency			3 (2.6%)	2 (2.2%)	
	Nocturia				2 (2.2%)	
<b>Gastrointestinal</b>	Nausea			4 (3.4%)	2 (2.2%)	
	Gastroenteritis/colitis	3 (2.5%)				
<b>Skin</b>	Pruritus			3 (2.6%)		
	Clamminess				4 (4.4%)*	
	Night sweats				3 (3.3%)*	3 (2.7%)*
	Alopecia				2 (2.2%)	
<b>Musculoskeletal</b>	Arthralgia			4 (3.4%)		
	Myalgia				2 (2.2%)	5 (4.5%)
	Pain in limb					3 (2.7%)
<b>Reproductive</b>	Testicular atrophy	6 (5.0%)			4 (4.4%)*	8 (7.2%)*
	Gynecomastia				2 (2.2%)*	4 (3.6%)*
	Testicular pain				2 (2.2%)	
<b>Psychiatric</b>	Decreased libido				3 (3.3%)*	

\*Expected pharmacological consequences of testosterone suppression.

In the patient populations studied with ELIGARD® 7.5 mg, a total of 86 hot flashes/sweats adverse events were reported in 70 patients. Of these, 71 events (83%) were mild; 14 (16%) were moderate; 1 (1%) was severe.

In the patient population studied with ELIGARD® 22.5 mg, a total of 84 hot flashes/sweats adverse events were reported in 66 patients. Of these, 73 events (87%) were mild; 11 (13%) were moderate; none were severe.

In the patient population studied with ELIGARD® 30 mg, a total of 75 hot flash adverse events were reported in 66 patients. Of these, 57 events (76%) were mild; 16 (21%) were moderate; 2 (3%) were severe.

In the patient population studied with ELIGARD® 45 mg, a total of 89 hot flash adverse events were reported in 64 patients. Of these, 62 events (70%) were mild; 27 (30%) were moderate; none were severe.

In addition, the following possibly or probably related systemic adverse events were reported by < 2% of the patients treated with ELIGARD® in these clinical studies.

<b>Body system</b>	<b>Adverse event</b>
General	Sweating, insomnia, syncope, rigors, weakness, lethargy
Gastrointestinal	Flatulence, constipation, dyspepsia
Hematologic	Decreased red blood cell count, hematocrit and hemoglobin
Metabolic	Weight gain
Musculoskeletal	Tremor, backache, joint pain, muscle atrophy, limb pain
Nervous	Disturbance of smell and taste, depression, vertigo
Psychiatric	Insomnia, depression, loss of libido*
Renal/urinary	Difficulties with urination, pain on urination, scanty urination, bladder spasm, blood in urine, urinary retention, urinary urgency, incontinence, nocturia, nocturia aggravated
Reproductive/ Urogenital:	Testicular soreness/pain, impotence*, decreased libido*, gynecomastia*, breast soreness/tenderness*, testicular atrophy*, erectile dysfunction, penile disorder*, reduced penis size
Skin	Alopecia, clamminess, night sweats*, sweating increased*
Vascular	Hypertension, hypotension

\* Expected pharmacological consequences of testosterone suppression.

**Changes in Bone Density:** Decreased bone density has been reported in the medical literature in men who have had orchiectomy or who have been treated with a GnRH agonist analog. It can be anticipated that long periods of medical castration in men will have effects on bone density.

## 6.2 Postmarketing experience

During post-marketing surveillance, rare cases of pituitary apoplexy (a clinical syndrome secondary to infarction of the pituitary gland) have been reported after the administration of gonadotropin-releasing hormone agonists. In a majority of these cases, a pituitary adenoma was diagnosed with a majority of pituitary apoplexy cases occurring within 2 weeks of the first dose, and some within the first hour. In these cases, pituitary apoplexy has presented as sudden headache, vomiting, visual changes, ophthalmoplegia, altered mental status, and sometimes cardiovascular collapse. Immediate medical attention has been required.

Convulsions have also been reported in the postmarketing setting.

## 7. DRUG INTERACTIONS

No pharmacokinetic drug-drug interaction studies were conducted with ELIGARD®.

## 8. USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

**Pregnancy category X.** [See 'Contraindications' section]

ELIGARD<sup>®</sup> is contraindicated in women who are or may become pregnant while receiving the drug. Expected hormonal changes that occur with ELIGARD<sup>®</sup> treatment increase the risk for pregnancy loss. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to the fetus and the potential risk for pregnancy loss.

In non-clinical studies in rats, major fetal abnormalities were observed after administration of leuprolide acetate throughout gestation. There were increased fetal mortality and decreased fetal weights in rats and rabbits. The effects of fetal mortality are expected consequences of the alterations in hormonal levels brought about by this drug. The possibility exists that spontaneous abortion may occur.

### 8.3 Nursing Mothers:

ELIGARD<sup>®</sup> is not indicated for use in women [*see Indications and Usage (1)*]. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ELIGARD<sup>®</sup>, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

### 8.4 Pediatric Use

The safety and effectiveness of ELIGARD<sup>®</sup> in pediatric patients have not been established.

### 8.5 Geriatric Use

The majority of the patients (approximately 70%) studied in the clinical trials were age 70 and older.

## 10. OVERDOSAGE

In clinical trials using daily subcutaneous injections of leuprolide acetate in patients with prostate cancer, doses as high as 20 mg/day for up to two years caused no adverse effects differing from those observed with the 1 mg/day dose.

## 11. DESCRIPTION

ELIGARD<sup>®</sup> is a sterile polymeric matrix formulation of leuprolide acetate, a GnRH agonist, for subcutaneous injection. It is designed to deliver leuprolide acetate at a controlled rate over a one-, three-, four- or six-month therapeutic period.



**Table 5. ELIGARD® Delivery System Composition and Constituted Product Formulation**

ELIGARD®		7.5 mg	22.5 mg	30 mg	45 mg
ATRIGEL® Delivery System syringe	Polymer	PLGH	PLG	PLG	PLG
	Polymer description	Copolymer containing carboxyl endgroups	Copolymer with hexanediol	Copolymer with hexanediol	Copolymer with hexanediol
	Polymer DL-lactide to glycolide molar ratio	50:50	75:25	75:25	85:15
Constituted product	Polymer delivered	82.5 mg	158.6 mg	211.5 mg	165 mg
	NMP delivered	160.0 mg	193.9 mg	258.5 mg	165 mg
	Leuprolide acetate delivered	7.5 mg	22.5 mg	30 mg	45 mg
	Approximate Leuprolide free base equivalent	7.0 mg	21 mg	28 mg	42 mg
	Approximate administered formulation weight	250 mg	375 mg	500 mg	375 mg
	Approximate injection volume	0.25 mL	0.375 mL	0.5 mL	0.375 mL

## 12. CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Leuprolide acetate, a gonadotropin releasing hormone (GnRH) agonist, acts as a potent inhibitor of gonadotropin secretion when given continuously in therapeutic doses. Animal and human studies indicate that after an initial stimulation, chronic administration of leuprolide acetate results in suppression of testicular and ovarian steroidogenesis. This effect is reversible upon discontinuation of drug therapy.

In humans, administration of leuprolide acetate results in an initial increase in circulating levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH), leading to a transient increase in levels of the gonadal steroids (testosterone and dihydrotestosterone in males, and estrone and estradiol in premenopausal females). However, continuous administration of leuprolide acetate results in decreased levels of LH and FSH. In males, testosterone is reduced to below castrate threshold ( $\leq 50$  ng/dL). These decreases occur within two to four weeks after initiation of treatment. Long-term studies have shown that continuation of therapy with leuprolide acetate maintains testosterone below the castrate level for up to seven years.

## 12.2 Pharmacodynamics

Following the first dose of ELIGARD<sup>®</sup>, mean serum testosterone concentrations transiently increased, then fell to below castrate threshold ( $\leq 50$  ng/dL) within three weeks for all ELIGARD<sup>®</sup> concentrations.

Continued monthly treatment with ELIGARD<sup>®</sup> 7.5 mg maintained castrate testosterone suppression throughout the study. No breakthrough of testosterone concentrations above castrate threshold ( $> 50$  ng/dL) occurred at any time during the study once castrate suppression was achieved (Figure 18).

One patient received less than a full dose of ELIGARD<sup>®</sup> 22.5 mg at baseline, never suppressed and withdrew from the study at Day 73. Of the 116 patients remaining in the study, 115 (99%) had serum testosterone levels below the castrate threshold by Month 1 (Day 28). By Day 35, 116 (100%) had serum testosterone levels below the castrate threshold. Once testosterone suppression was achieved, one patient ( $< 1\%$ ) demonstrated breakthrough (concentrations  $> 50$  ng/dL after achieving castrate levels) following the initial injection; that patient remained below the castrate threshold following the second injection (Figure 19).

One patient withdrew from the ELIGARD<sup>®</sup> 30 mg study at Day 14. Of the 89 patients remaining in the study, 85 (96%) had serum testosterone levels below the castrate threshold by Month 1 (Day 28). By Day 42, 89 (100%) of patients attained castrate testosterone suppression. Once castrate testosterone suppression was achieved, three patients (3%) demonstrated breakthrough (concentrations  $> 50$  ng/dL after achieving castrate levels) (Figure 20).

One patient at Day 1 and another patient at Day 29 were withdrawn from the ELIGARD<sup>®</sup> 45 mg study. Of the 109 patients remaining in the study, 108 (99.1%) had serum testosterone levels below the castrate threshold by Month 1 (Day 28). One patient did not achieve castrate suppression and was withdrawn from the study at Day 85. Once castrate testosterone suppression was achieved, one patient ( $< 1\%$ ) demonstrated breakthrough (concentrations  $> 50$  ng/dL after achieving castrate levels) (Figure 21).

Leuprolide acetate is not active when given orally.

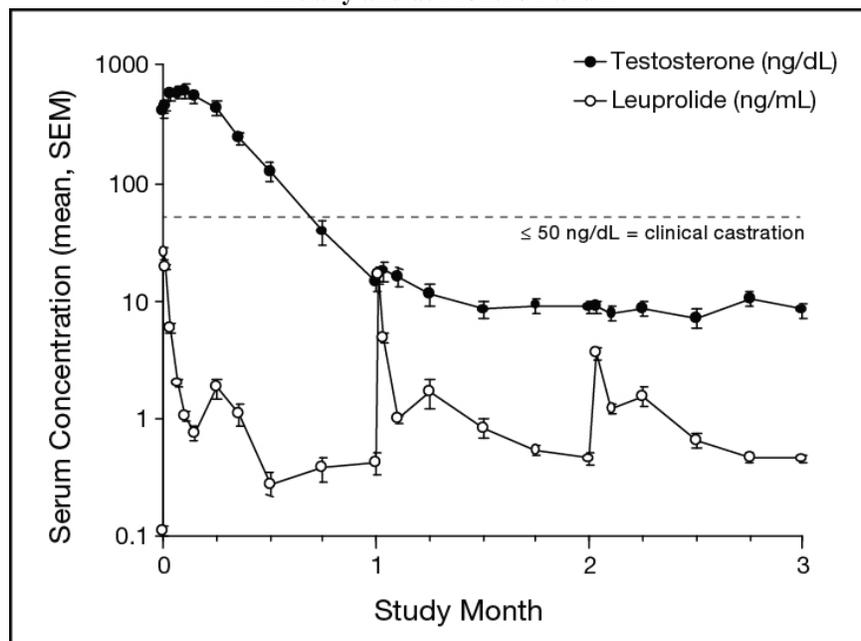
## 12.3 Pharmacokinetics

### Absorption

#### *ELIGARD<sup>®</sup> 7.5 mg*

The pharmacokinetics/pharmacodynamics observed during three once-monthly injections in 20 patients with advanced prostate cancer is shown in Figure 18. Mean serum leuprolide concentrations following the initial injection rose to 25.3 ng/mL ( $C_{max}$ ) at approximately 5 hours after injection. After the initial increase following each injection, serum concentrations remained relatively constant (0.28 – 2.00 ng/mL).

**Figure 18. Pharmacokinetic/Pharmacodynamic Response (N=20) to ELIGARD® 7.5 mg – Patients Dosed Initially and at Months 1 and 2**

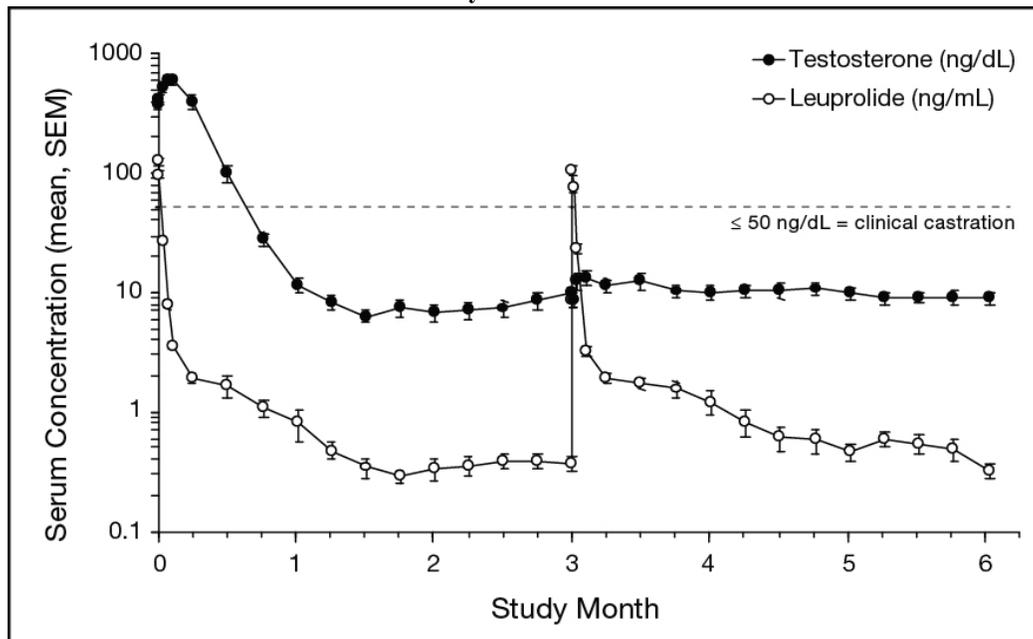


A reduced number of sampling time points resulted in the apparent decrease in  $C_{max}$  values with the second and third doses of ELIGARD® 7.5 mg (Figure 18).

#### *ELIGARD® 22.5 mg*

The pharmacokinetics/pharmacodynamics observed during two injections every three months (ELIGARD® 22.5 mg) in 22 patients with advanced prostate cancer is shown in Figure 19. Mean serum leuprolide concentrations rose to 127 ng/mL and 107 ng/mL at approximately 5 hours following the initial and second injections, respectively. After the initial increase following each injection, serum concentrations remained relatively constant (0.2 – 2.0 ng/mL).

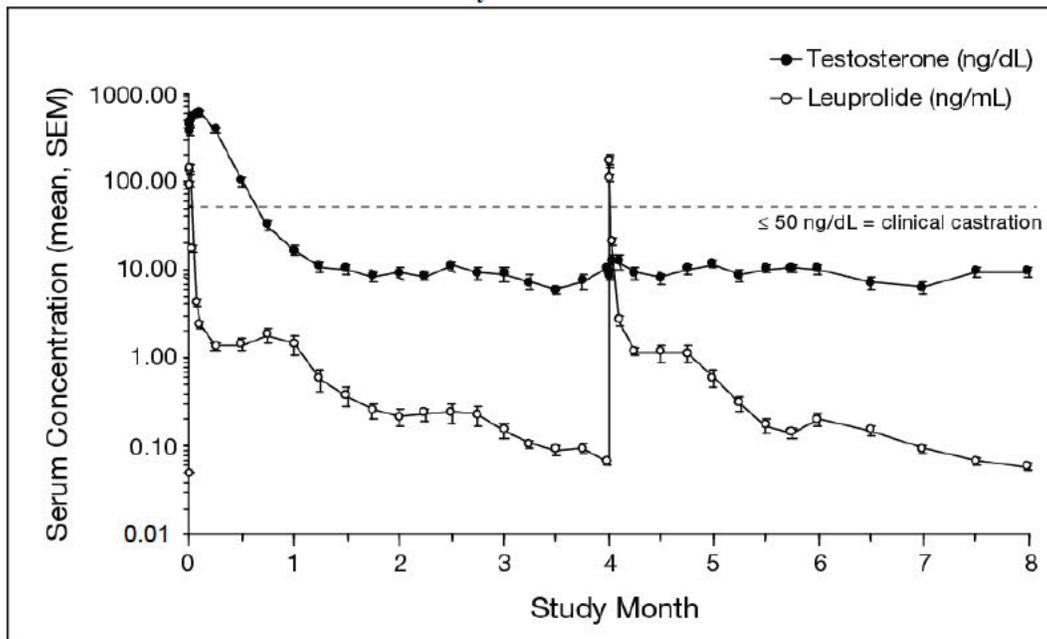
**Figure 19. Pharmacokinetic/Pharmacodynamic Response (N=22) to ELIGARD® 22.5 mg – Patients Dosed Initially and at Month 3**



*ELIGARD® 30 mg*

The pharmacokinetics/pharmacodynamics observed during injections administered initially and at four months (ELIGARD® 30 mg) in 24 patients with advanced prostate cancer is shown in Figure 20. Mean serum leuprolide concentrations following the initial injection rose rapidly to 150 ng/mL ( $C_{max}$ ) at approximately 3.3 hours after injection. After the initial increase following each injection, mean serum concentrations remained relatively constant (0.1 – 1.0 ng/mL).

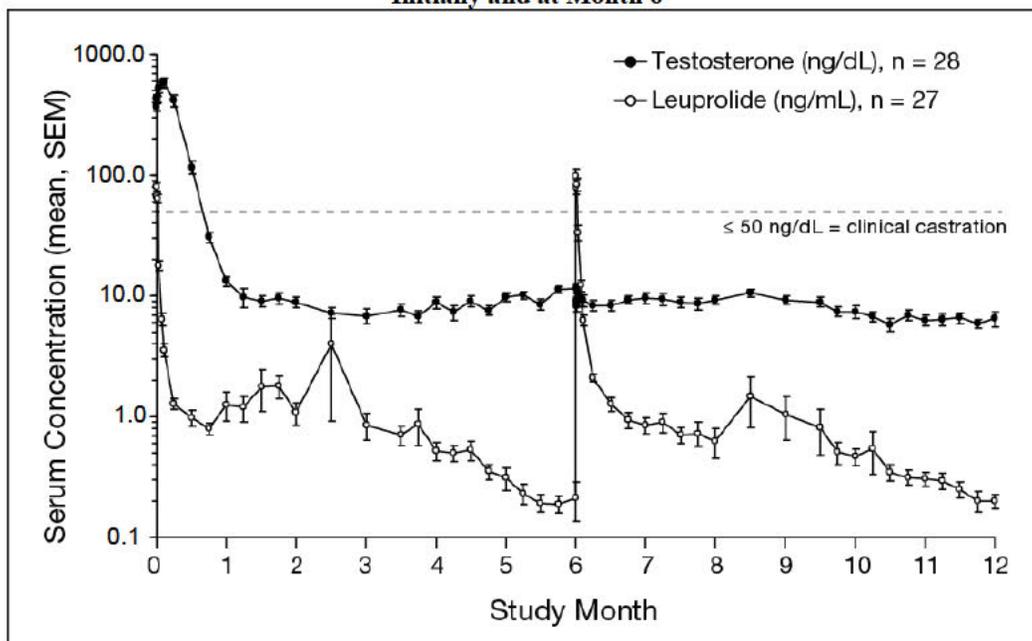
**Figure 20. Pharmacokinetic/Pharmacodynamic Response (N=24) to ELIGARD® 30 mg – Patients Dosed Initially and at Month 4**



*ELIGARD® 45 mg*

The pharmacokinetics/pharmacodynamics observed during injections administered initially and at six months (ELIGARD® 45 mg) in 27 patients with advanced prostate cancer is shown in Figure 21. Mean serum leuprolide concentrations rose to 82 ng/mL and 102 ng/mL ( $C_{max}$ ) at approximately 4.5 hours following the initial and second injections, respectively. After the initial increase following each injection, mean serum concentrations remained relatively constant (0.2 – 2.0 ng/mL).

**Figure 21. Pharmacokinetic/Pharmacodynamic Response (N=27) to ELIGARD® 45 mg - Patients Dosed Initially and at Month 6**



There was no evidence of significant accumulation during repeated dosing. Non-detectable leuprolide plasma concentrations have been occasionally observed during ELIGARD® administration, but testosterone levels were maintained at castrate levels.

**Distribution.** The mean steady-state volume of distribution of leuprolide following intravenous bolus administration to healthy male volunteers was 27 L. In vitro binding to human plasma proteins ranged from 43% to 49%.

**Metabolism.** In healthy male volunteers, a 1-mg bolus of leuprolide administered intravenously revealed that the mean systemic clearance was 8.34 L/h, with a terminal elimination half-life of approximately 3 hours based on a two compartment model.

No drug metabolism study was conducted with ELIGARD®. Upon administration with different leuprolide acetate formulations, the major metabolite of leuprolide acetate is a pentapeptide (M-1) metabolite.

**Excretion.** No drug excretion study was conducted with ELIGARD®.

**Geriatrics.** [see USE IN SPECIAL POPULATIONS (8.5)]

**Race.** In patients studied, mean serum leuprolide concentrations were similar regardless of race. Refer to Table 6 for distribution of study patients by race.

**Table 6. Race Characterization of ELIGARD® Study Patients**

<b>Race</b>	<b>ELIGARD® 7.5 mg</b>	<b>ELIGARD® 22.5 mg</b>	<b>ELIGARD® 30 mg</b>	<b>ELIGARD® 45 mg</b>
White	26	19	18	17
Black	-	4	4	7
Hispanic	2	2	2	3

**Renal and Hepatic Insufficiency.** The pharmacokinetics of ELIGARD® in hepatically and renally impaired patients have not been determined.

## 13. NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year carcinogenicity studies were conducted with leuprolide acetate in rats and mice. In rats, a dose-related increase of benign pituitary hyperplasia and benign pituitary adenomas was noted at 24 months when the drug was administered subcutaneously at high daily doses (0.6 to 4 mg/kg). There was a significant but not dose-related increase of pancreatic islet-cell adenomas in females and of testicular interstitial cell adenomas in males (highest incidence in the low dose group). In mice, no leuprolide acetate-induced tumors or pituitary abnormalities were observed at a dose as high as 60 mg/kg for two years. Patients have been treated with leuprolide acetate for up to three years with doses as high as 10 mg/day and for two years with doses as high as 20 mg/day without demonstrable pituitary abnormalities. No carcinogenicity studies have been conducted with ELIGARD®.

Mutagenicity studies have been performed with leuprolide acetate using bacterial and mammalian systems and with ELIGARD® 7.5 mg in bacterial systems. These studies provided no evidence of a mutagenic potential.

## 14. CLINICAL STUDIES

One open-label, multicenter study was conducted with each ELIGARD® formulation (7.5 mg, 22.5 mg, 30 mg, and 45 mg) in patients with Jewett stage A through D prostate cancer who were treated with at least a single injection of study drug (Table 7). These studies evaluated the achievement and maintenance of castrate serum testosterone suppression over the duration of therapy (Figures 22-25).

During the AGL9904 study using ELIGARD® 7.5 mg, once testosterone suppression was achieved, no patients (0%) demonstrated breakthrough (concentration >50 ng/dL) at any time in the study.

During the AGL9909 study using ELIGARD<sup>®</sup> 22.5 mg, once testosterone suppression was achieved, only one patient (< 1%) demonstrated breakthrough following the initial injection; that patient remained below the castrate threshold following the second injection.

During the AGL0001 study using ELIGARD<sup>®</sup> 30 mg, once testosterone suppression was achieved, three patients (3%) demonstrated breakthrough. In the first of these patients, a single serum testosterone concentration of 53 ng/dL was reported on the day after the second injection. In this patient, castrate suppression was reported for all other time points. In the second patient, a serum testosterone concentration of 66 ng/dL was reported immediately prior to the second injection. This rose to a maximum concentration of 147 ng/dL on the second day after the second injection. In this patient, castrate suppression was again reached on the seventh day after the second injection and was maintained thereafter. In the final patient, serum testosterone concentrations > 50 ng/dL were reported at 2 and at 8 hours after the second injection. Serum testosterone concentration rose to a maximum of 110 ng/dL on the third day after the second injection. In this patient, castrate suppression was again reached eighteen days after the second injection and was maintained until the final day of the study, when a single serum testosterone concentration of 55 ng/dL was reported.

During the AGL0205 study using ELIGARD<sup>®</sup> 45 mg, once testosterone suppression was achieved, one patient (<1%) demonstrated breakthrough. This patient reached castrate suppression at Day 21 and remained suppressed until Day 308 when his testosterone level rose to 112 ng/dL. At Month 12 (Day 336), his testosterone was 210 ng/dL.

**Table 7. Summary of ELIGARD® Clinical Studies**

ELIGARD®		7.5 mg	22.5 mg	30 mg	45 mg
<b>Study number</b>		AGL9904	AGL9909	AGL0001	AGL0205
<b>Total number of patients</b>		120 (117 completed)	117 <sup>2</sup> (111 completed <sup>3</sup> )	90 (82 completed <sup>4</sup> )	111 (103 completed <sup>5</sup> )
<b>Jewett stages</b>	Stage A	-	2	2	5
	Stage B	-	19	38	43
	Stage C	89	60	16	19
	Stage D	31	36	34	44
<b>Treatment</b>		6 monthly injections	1 injection (4 patients) 2 injections, one every three months (113 patients)	1 injection (5 patients) 2 injections, one every four months (85 patients)	1 injection (5 patients) 2 injections, one every six months (106 patients)
<b>Duration of therapy</b>		6 months	6 months	8 months	12 months
<b>Mean testosterone concentration (ng/dL)</b>	Baseline	361.3	367.1	385.5	367.7
	Day 2	574.6 (Day 3)	588.0	610.0	588.6
	Day 14	Below Baseline (Day 10)	Below Baseline	Below Baseline	Below Baseline
	Day 28	21.8	27.7 (Day 21)	17.2	16.7
	Conclusion	6.1	10.1	12.4	12.6
<b>Number of patients below castrate threshold (≤ 50 ng/dL)</b>	Day 28	112 of 119 (94.1%)	115 of 116 (99%)	85 of 89 (96%)	108 of 109 (99.1%)
	Day 35	-	116 (100%)	-	-
	Day 42	119 (100%)	-	89 (100%)	-
	Conclusion	117 <sup>1</sup> (100%)	111 (100%)	81 (99%)	102 (99%)

1. Two patients withdrew for reasons unrelated to drug.
2. One patient received less than a full dose at Baseline, never suppressed, and was withdrawn at Day 73 and given an alternate treatment.
3. All non-evaluable patients who attained castration by Day 28 maintained castration at each time point up to and including the time of withdrawal.
4. One patient withdrew on Day 14. All 7 non-evaluable patients who had achieved castration by Day 28 maintained castration at each time point, up to and including the time of withdrawal.
5. Two patients were withdrawn prior to the Month 1 blood draw. One patient did not achieve castration and was withdrawn on Day 85. All 5 non-evaluable patients who attained castration by Day 28, maintained castration at each time point up to and including the time of withdrawal.

Figure 22. ELIGARD® 7.5 mg Mean Serum Testosterone Concentrations (n=117)

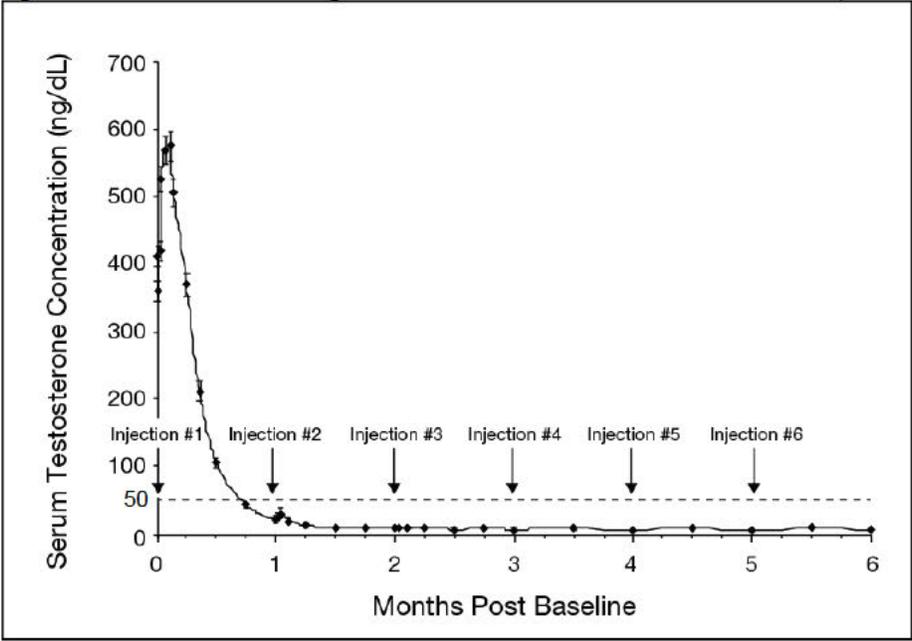
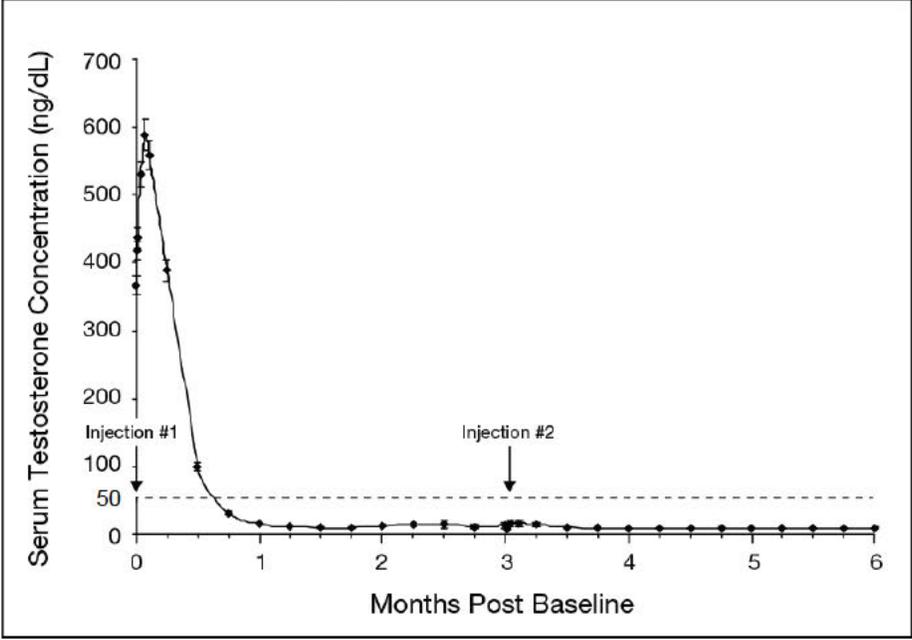
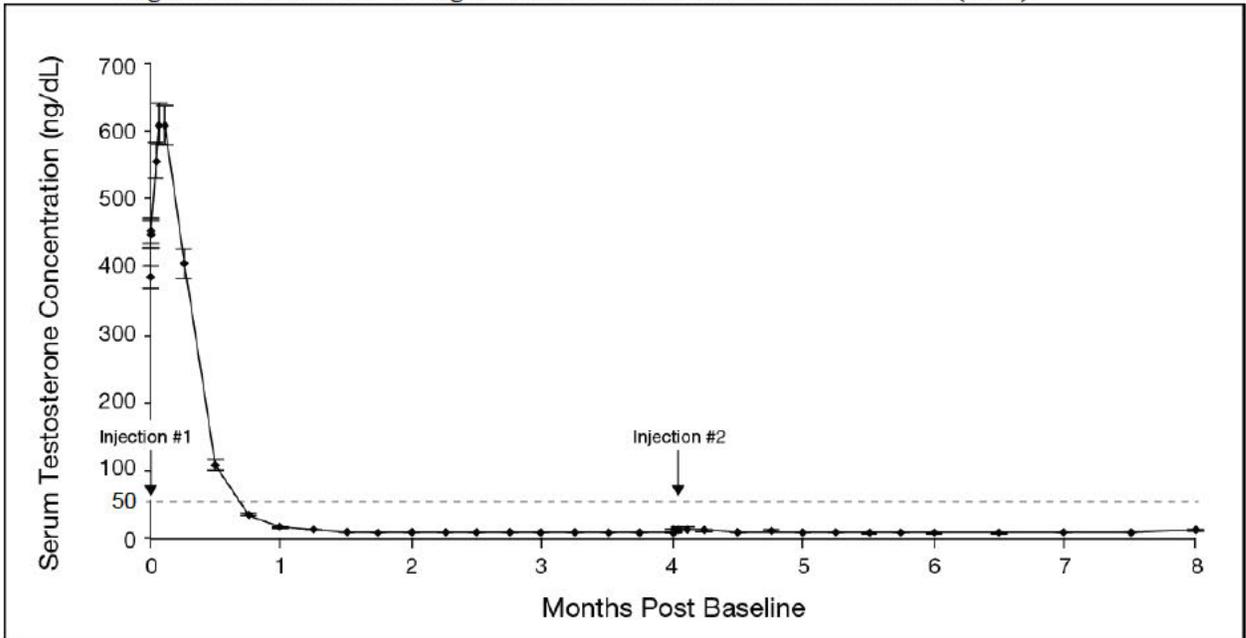


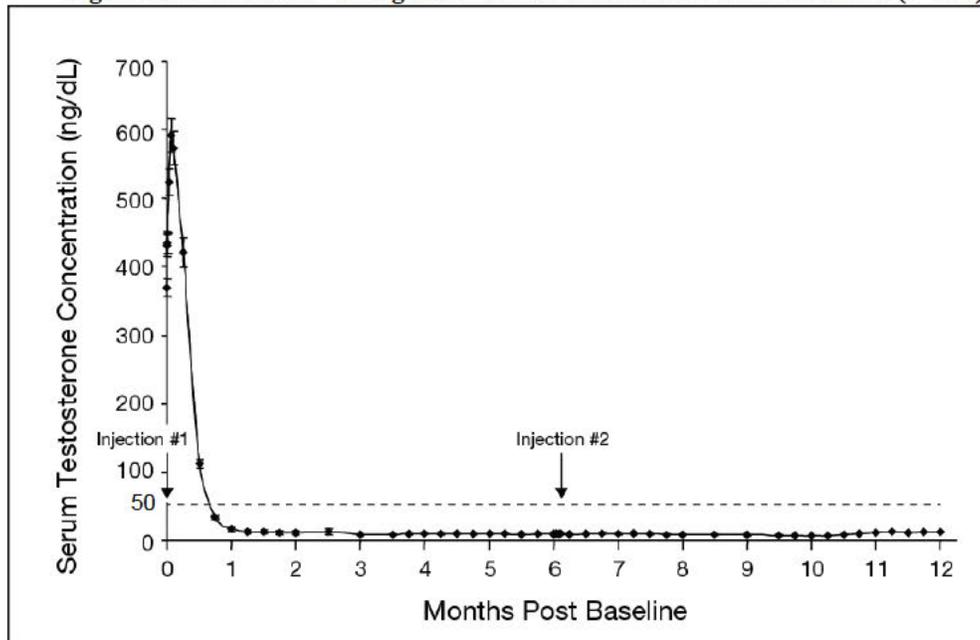
Figure 23. ELIGARD® 22.5 mg Mean Serum Testosterone Concentrations (n=111)



**Figure 24. ELIGARD® 30 mg Mean Serum Testosterone Concentrations (n=90)**



**Figure 25. ELIGARD® 45 mg Mean Serum Testosterone Concentrations (n=103)**



Serum PSA decreased in all patients in all studies whose Baseline values were elevated above the normal limit. Refer to Table 8 for a summary of the effectiveness of ELIGARD® in reducing serum PSA values.

**Table 8. Effect of ELIGARD® on Patient Serum PSA Values**

<b>ELIGARD®</b>	<b>7.5 mg</b>	<b>22.5 mg</b>	<b>30 mg</b>	<b>45 mg</b>
Mean PSA reduction at study conclusion	94%	98%	86%	97%
Patients with normal PSA at study conclusion*	94%	91%	93%	95%

\*Among patients who presented with elevated levels at Baseline

Other secondary efficacy endpoints evaluated included WHO performance status, bone pain, urinary pain and urinary signs and symptoms. Refer to Table 9 for a summary of these endpoints.

**Table 9. Secondary Efficacy Endpoints**

<b>ELIGARD®</b>		<b>7.5 mg</b>	<b>22.5 mg</b>	<b>30 mg</b>	<b>45 mg</b>
<b>Baseline</b>	WHO Status = 0 <sup>1</sup>	88%	94%	90%	90%
	WHO Status = 1 <sup>2</sup>	11%	6%	10%	7%
	WHO Status = 2 <sup>3</sup>				3%
	Mean bone pain <sup>4</sup> (range)	1.22 (1-9)	1.20 (1-9)	1.20 (1-7)	1.38 (1-7)
	Mean urinary pain (range)	1.12 (1-5)	1.02 (1-2)	1.01 (1-2)	1.22 (1-8)
	Mean urinary signs and symptoms (range)	Low	1.09 (1-4)	Low	Low
	Number of patients with prostate abnormalities	102 (85%)	96 (82%)	66 (73%)	89 (80%)
		<b>Month 6</b>	<b>Month 6</b>	<b>Month 8</b>	<b>Month 12</b>
<b>Follow-up</b>	WHO status = 0	Unchanged	96%	87%	94%
	WHO status = 1	Unchanged	4%	12%	5%
	WHO status = 2			1%	1%
	Mean bone pain (range)	1.26 (1-7)	1.22 (1-5)	1.19 (1-8)	1.31 (1-8)
	Mean urinary pain (range)	1.07 (1-8)	1.10 (1-8)	1.00 (1-1)	1.07 (1-5)
	Mean urinary signs and symptoms (range)	Modestly decreased	1.18 (1-7)	Modestly decreased	Modestly decreased
	Number of patients with prostate abnormalities	77 (64%)	76 (65%)	54 (60%)	60 (58%)

1. WHO status = 0 classified as “fully active.”

2. WHO status = 1 classified as “restricted in strenuous activity but ambulatory and able to carry out work of a light or sedentary nature.”

3. WHO status = 2 classified as “ambulatory but unable to carry out work activities.”

4. Pain score scale: 1 (no pain) to 10 (worst pain possible).

## 15. REFERENCES

1. “OSHA Hazardous Drugs.” *OSHA*. <http://www.osha.gov/SLTC/hazardousdrugs/index.html>

## 16. HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How supplied

ELIGARD<sup>®</sup> is available in a single use kit of a two syringe-mixing system with a sterile needle in the following strengths:

ELIGARD<sup>®</sup> 7.5 mg – NDC 62935-752-75

ELIGARD<sup>®</sup> 22.5 mg – NDC 62935-222-05

ELIGARD<sup>®</sup> 30 mg – NDC 62935-302-30

ELIGARD<sup>®</sup> 45 mg – NDC 62935-452-45

ELIGARD<sup>®</sup> is available in a single use kit of a two syringe-mixing system with a sterile safety needle in the following strengths:

ELIGARD<sup>®</sup> 7.5 mg – NDC 62935-753-75

ELIGARD<sup>®</sup> 22.5 mg – NDC 62935-223-05

ELIGARD<sup>®</sup> 30 mg – NDC 62935-303-30

ELIGARD<sup>®</sup> 45 mg – NDC 62935-453-45

### 16.2 Storage:

Store at 2 - 8 °C (35.6 – 46.4 °F)

Once outside the refrigerator this product may be stored in its original packaging at room temperature 15 – 30 °C (59 – 86 °F) for up to eight weeks prior to mixing and administration.

## 17. PATIENT COUNSELING INFORMATION

As with other GnRH agonists, patients may experience hot flashes. During the first few weeks of treatment, patients may also experience increased bone pain, increased difficulty in urinating, and the onset or aggravation of weakness or paralysis. Patients should notify their doctor if they develop new or worsened symptoms after beginning ELIGARD<sup>®</sup> treatment. Patients should be told about the injection site related adverse reactions, such as transient burning/stinging, pain, bruising, and redness. These injection site reactions are usually mild and reversible. If they do not resolve, patients should tell their doctor. If the patient experiences an allergic reaction, they should contact their doctor immediately.

**Rx only**

Revised 02/2016

Manufactured by: TOLMAR Inc.  
Fort Collins, CO 80526  
for: TOLMAR Therapeutics, Inc.  
Fort Collins, CO 80526

Distributed by: TOLMAR Pharmaceuticals, Inc.  
Fort Collins, CO 80526

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04005921 Rev. 1 02/16

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 21343/S33**

**OTHER REVIEW(S)**

**Division of Oncology Products 1**

**REGULATORY PROJECT MANAGER LABELING REVIEW**

**Application:** NDA 021343/S-033, NDA 021379/S-033, NDA 021488/S-030,  
NDA 021731/S-029

**Name of Drug:** Eligard<sup>®</sup> (leuprolide acetate for injectable solution), 7.5 mg, 22.5 mg, 30 mg,  
45 mg

**Applicant:** TOLMAR Therapeutics, Inc.

**Labeling Reviewed**

**Submission Date:** September 23, 2015

**Receipt Date:** September 23, 2015

**Background and Summary Description:**

These supplemental applications, submitted as "Prior Approval Supplement", are submitted to add room temperature storage information in Section 2 (Dosage and Administration) and in subsection 16.2 (Storage) to allow for flexibility when prescribing, preparing and administering the product to the patient. Additional editorial revisions are proposed throughout the label for clarity.

These supplements were also reviewed by Yang-Min (Max) Ning, MD, Clinical Reviewer (See Clinical review in DARRTS dated February 26, 2016), Lorenzo Rocca, PhD, CMC Reviewer (See CMC review in DARRTS dated February 8, 2016), and Tingting Gao, PhD, DMEPA Reviewer (See DMEPA review in DARRTS dated October 23, 2015). Because the label is a rearrangement of existing data, DOP1's Director requested that most of the labeling discussions be conducted via e-mail. However, one face-to-face meeting was conducted between the clinical team and DMEPA to go over the Instructions for Use section of the label. This meeting took place on January 20, 2016.

**Recommendation**

These SLRs can be approved based on the Division's review and discussion via email and during the January 20, 2016, internal labeling meeting where division disciplines noted above and division management attended.

Rajesh Venugopal, MPH, MBA  
Regulatory Project Manager

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Christy Cottrell  
Chief, Project Management Staff

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**Review**

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/s/  
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RAJESH VENUGOPAL  
02/29/2016

CHRISTY L COTTRELL  
02/29/2016

## Clinical Review of Labeling Revisions for Eligard

NDA/Number(s)/Submission: NDA 021343 (Supplement-033) and related NDAs (021379, 021488, 021731)

Drug Name: ELIGARD® 7.5 mg, 22.5 mg, 30 mg, and 45 mg (leuprolide acetate for injectable suspension)

Indication: Palliative treatment of advanced prostate cancer

Sponsor: TOLMAR Inc.

Date Submitted: 09/23/2015

Date Completed: 02/08/2016

Medical Officer: Yang-Min (Max) Ning MD, PhD

### SUMMARY:

(1) Is any action necessary based on the proposed labeling revisions: Yes:  No:

(a) If yes, please identify the basis for the necessary action:

i. New labeling content and format: Yes:  No:

*To modify and improve the Instructions for Use*

ii. Addition of Section of patient counseling information: Yes:  No:

iii. Addition of new adverse events identified during post-approval safety monitoring:  
Yes:  No:

(b) Is follow-up by the RPM indicated: Yes:  No:

(c) Is a Labeling Consult recommended: Yes:  No:

*DMEPA was consulted regarding the proposed revisions.*

### Review Comments

This supplement for the four approved strengths of ELIGARD proposed to add a range of room temperature for storage in Section 16.2 and to clarify Instructions for Use in Section 2 of the package insert. The new storage information and statement were reviewed by the CMC team and found acceptable. The proposed changes in Instructions for Use were reviewed by the clinical team with

feedback from the DMEPA team. We had the following recommendations conveyed to the applicant. On January 28, 2016, the applicant acknowledged and implemented all the recommended changes.

- Emphasize its subcutaneous administration route by bolding the word **subcutaneous** at the beginning of Section 2.2. This may help distinguish it from Lupron, which has the same active ingredient (leuprolide) but is administered intramuscularly.
- Add “or it should be discarded” in the sentence “Once mixed, the product must be administered within 30 minutes” under Administration Procedure.
- Change the word “(b) (4)” in Section 16.2 to “mixing and administration”. This makes this part consistent with the information in Section 2.2.

In addition, this review identified an issue concerning whether the 90 degree needle insertion as shown in Section 2.2 may be associated with a risk of injecting Eligard into the abdominal muscle and/or peritoneal cavity. The applicant clarified that this administration instruction was used in the clinical trials supporting the approval and that the products have been successfully marketed for >10 years with millions of injections administered. The applicant reasoned that the effect of administration at other degrees (e.g. at 45 degree) has not been studied in any of the clinical programs, including the impact on the polymer bolus, bolus biodegradation, and possible effects on the PK release patterns. The DMEPA review team searched the ISMP newsletters and retrieved no medication errors or actions possibly associated with Eligard. Given these facts and applicant’s concern, keeping the original needle insertion at 90 degree in the label appears appropriate. Additional studies would be needed if considerable administration-associated medical errors emerge in the pharmacovigilance program for Eligard.

This supplement had no changes in the efficacy and safety data about Eligard.

See the final approved label for more details regarding the revisions introduced with this review.

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/s/  
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YANGMIN NING  
02/25/2016

VIRGINIA E MAHER  
02/26/2016

CHEMISTRY REVIEW  
OF **BUNDLED LABELING**  
**SUPPLEMENT**

1. ORGANIZATION: OPQ – Office of Lifecycle Drug Product (OLDP)

2. NDA Number: **21343 (lead)** **21379/S033**

3. SUPPLEMENT NUMBERS/DATES: **S033 (PAS)** **21488/S030**  
**21731/S029**

Letter date: **Sept. 23, 2015** **Sept. 23, 2015**

Stamp date: **Sept. 23, 2015** **Sept. 23, 2015**

4. AMENDMENTS/REPORTS/DATES: **Amendment (SDN254)**

Letter date: **Jan. 28, 2016** **Jan. 28, 2016**

Stamp date: **Jan. 28, 2016** **Jan. 28, 2016**

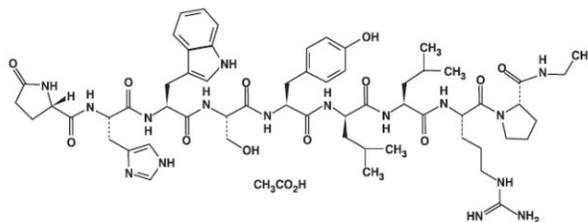
5. RECEIVED BY CHEMIST: **Oct. 1, 2015**

6. APPLICANT NAME & ADDRESS Tolmar Therapeutics, Inc.  
701 Centre Avenue  
Fort Collins, CO 80526

7. NAME OF DRUG: Eligard®

8. NONPROPRIETARY NAME: leuprolide

9. CHEMICAL NAME/STRUCTURE: 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate (salt)  
 $C_{59}H_{84}N_{16}O_{12}$ ; MW: 1269.4



10. DOSAGE FORM(S): Injectable suspension, subcutaneous

11. POTENCY: 7.5 mg (**21343**), 22.5mg (**21379**), 30mg (**21488**) and 45mg (**21731**)

12. PHARMACOLOGICAL CATEGORY: Leuprolide acetate is a synthetic nonapeptide analog of naturally occurring gonadotropin releasing hormone (GnRH) that, when given continuously in therapeutic doses, inhibits pituitary gonadotropin secretion and suppresses testicular and ovarian steroidogenesis. Eligard is indicated for the palliative treatment of advanced prostate cancer.

13. HOW DISPENSED:       X       (R<sub>x</sub>)            (OTC)

14. RECORDS & REPORTS CURRENT:       X       Yes            No

REVIEW RECORDS & REPORTS CURRENT       X       Yes            No

15. RELATED IND/NDA/DMF: none

16. SUPPLEMENT PROVIDES FOR: The addition of a statement for room temperature storage for up to eight weeks prior to reconstitution to the Eligard Prescribing Information (PI), and revisions throughout the PI to provide clarification of the Eligard PI.

17. COMMENTS: Tolmar Therapeutics, Inc. (Tolmar) NDA 21343 Eligard (leuprolide acetate for injectable suspension) was approved January 23, 2002. Tolmar has submitted a PAS, which proposes adding a Room Temperature Storage statement and other changes for clarification to the Eligard PI. On October 2, 2015, Rajesh Venugopal, MPH (Senior Regulatory Project Manager-Division of Oncology Products 1 (DOP1)), informed Tolmar that the proposed changes would reviewed as a PAS. Since the same changes will be made to all strengths of the drug product, the proposed changes will be reviewed as a bundled labeling supplement 21343/S033, 21379/S033, 21488/S030 and 21731/S029 with 21343/S033 designated as the lead

review (21343/S033 (Bundle)). This bundled PAS will be managed by DOP1/Office of Hematology and Oncology Products (OHOP).

### **Background/Introduction:**

Eligard is a sterile polymeric matrix formulation of leuprolide acetate. Eligard is injected subcutaneously where it forms a solid drug delivery depot, and provides continuous release of leuprolide acetate over a one-, three-, four-, or six-month treatment period. The injection delivers the dose of leuprolide acetate as indicated below:

Eligard Recommended Dosing

<b>Dosage/NDA</b>	7.5mg/21343	22.5mg/21379	30mg/21488	45mg/21731
<b>Recommended Dose</b>	1 injection every month	1 injection every 3 months	1 injection every 4 months	1 injection every 6 months

Tolmar is submitting 21343/S033 (Bundle) to add a room temperature storage statement. The proposed room temperature statement will be added to Section **16.2 Storage:** of the PI. Tolmar also proposes updating the pictures, text and table formatting in the PI to provide more clarity to the PI.

DOP1 requested an OSE consult review of these changes for areas of vulnerability that could lead to medication errors. On October 23, 2015, Dr. Tingting Gao, PharmD (Primary Reviewer, DMEPA /OSE) reviewed the proposed updated PI, and requested that the applicant correct inconsistencies in Section **2.2** and Section **16.2 Storage:**, with respect to Section **2.1**.

On January 20, 2016 the changes recommended by DMEPA along with the edits and comments from the 21343/S033 (Bundle) review team were sent to the applicant as an annotated PI word document. Tolmar was asked to make the changes accordingly, and return the final clean version of the PI.

On January 28, 2016, Tolmar amended (**SDN254**) 21343/S033 (Bundle) with the proposed Eligard PI in which they implemented all requested changes. The following room temperature statement will be added to Section **16.2 Storage:** of the final PI.

*Once outside the refrigerator, this product may be stored in its original packaging at room temperature 15-30°C (59-86°F) for up to eight weeks prior to mixing and administration.*

#### **1.14.2.2 – Final Package Insert**

Tolmar has provided stability data on lots of Eligard 7.5, 22.5, 30 and 45mg in order to support the room temperature storage of Eligard for up to eight weeks. The lots are listed below along with the supplemental application in which they were initially submitted.

<b>Dosage/NDA</b>	<b>Stability Lot No.</b>	<b>Original Supplement Application</b>
7.5mg/21343	3710, 3710A, 4199	S017 ( approved April 16, 2010)
22.5mg/21379	3709, 3709A, 4106	S013 ( approved August 27, 2010)
30mg/21488	3769, 5064A1, 5068A1	S013 (approved July 16, 2010)
45mg/21731	4367, 4368, 4399	S009 (approved April 1, 2009)

These stability data are provided in Section **3.2.P.8.3** of 21343/S033 (Bundle).

The stability lots were stored at long term (5±3°C) until one month before expiry. Samples were then transferred to room-temperature (25±2°C/60±5%RH) storage conditions and tested at one and two month intervals (24 month expiry and 25 months). All data for these lots met the currently approved drug product release and shelf life specifications. In addition, Tolmar has provided a listing of the supplemental CMC applications that have been submitted and approved since the supplements containing the supporting stability

data were approved. The CMC supplemental history for Eligard 7.5, 22.5, 30 and 45mg are such that the stability data from the lots listed above are applicable to Eligard drug product currently marketed.

The stability data adequately supports the proposed room temperature storage of Eligard 7.5, 22.5, 30 and 45mg drug product for up to eight weeks prior to mixing and administration. No other CMC changes are proposed in the revised Eligard PI.

**Overall Evaluation: Acceptable**

18. CONCLUSIONS & RECOMMENDATIONS: Recommend approval of 21343/S033 (Bundle) from a CMC perspective.

19. REVIEWER NAME	SIGNATURE	DATE COMPLETED
Lorenzo A. Rocca	Signed Electronically	

20. BRANCH CHIEF NAME	SIGNATURE	DATE COMPLETED
Ramesh Raghavachari	Signed Electronically	

cc:  
OLDP/RRaghavachari  
OLDP/LRocca  
PM/DOP1/RVenugopal

F/T by: LRocca, File:C: Data\LR\Supplement\n21343\_21379\_21488\_21731pm\S033(PAS)\21343\_S-033Review1.doc

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## LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

**\*\*\* This document contains proprietary information that cannot be released to the public\*\*\***

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<b>Date of This Review:</b>	October 23, 2015
<b>Requesting Office or Division:</b>	Division of Oncology Products 1 (DOP1)
<b>Application Type and Number:</b>	NDA 021343/S-033, NDA 021379/S-033, NDA 021488/S-030, NDA 021731/S-029
<b>Product Name and Strength:</b>	Eligard (leuprolide acetate) for injectable suspension, 7.5 mg, 22.5 mg, 30 mg, 45 mg
<b>Product Type:</b>	Single ingredient product
<b>Rx or OTC:</b>	Rx
<b>Applicant/Sponsor Name:</b>	Tolmar Therapeutics Inc.
<b>Submission Date:</b>	September 23, 2015
<b>OSE RCM #:</b>	2015-2204
<b>DMEPA Primary Reviewer:</b>	Tingting Gao, PharmD
<b>DMEPA Team Leader:</b>	Chi-Ming (Alice) Tu, PharmD

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## 1 REASON FOR REVIEW

Tolmar submitted prior approval supplements (PAS) for NDA 021343, NDA 021379, NDA 021488, and NDA 021731 to propose the addition of room temperature storage for up to eight weeks prior to reconstitution statement to the Eligard Prescribing Information. Tolmar provided the stability testing results to support this proposal.

The Division of Oncology Products 1 (DOP1) requested that we review the submitted proposed Prescribing Information (PI) labeling for areas of vulnerability that could lead to medication errors.

## 2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

<b>Material Reviewed</b>	<b>Appendix Section (for Methods and Results)</b>
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters	D
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

\*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

In this PAS, Tolmar proposed to re-format tables in Section 2 for consistency and clarity, update instructions in Sections 2.1 and 2.2 for clarity on mixing and administration procedures, and to update the storage statement in Section 16. We reviewed the proposed changes to these sections of the PI and found a few inconsistencies between the sections. We provide our recommendation in Section 4.1 below.

## 4 CONCLUSION & RECOMMENDATIONS

Our review of the proposed prescribing information (PI) found the proposed PI may be improved to further clarify the information.

#### 4.1 RECOMMENDATIONS FOR THE DIVISION

- A. Dosage and Administration section, Full PI
  - 1. Ensure the “IMPORTANT: Allow the product to reach...” statement in Section 2.2 Administration Procedure is consistent with the “IMPORTANT: Allow the product to reach...” statement in Section 2.1 Mixing Procedure by adding the statement “... or it should be discarded.”
- B. How Supplied/Storage and Handling section, Full PI
  - 1. Replace the word (b) (4) with “mixing and administration” to be consistent with the terminology used in the Section 2.1 Mixing Procedure in Dosage and Administration section of the PI.

## APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

### APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Eligard that Tolmar submitted on September 23, 2015.

<b>Table 2. Relevant Product Information for Eligard</b>	
<b>Initial Approval Date</b>	January 23, 2002
<b>Active Ingredient</b>	Leuprolide Acetate
<b>Indication</b>	Palliative treatment of advanced prostate cancer
<b>Route of Administration</b>	Subcutaneous Injection
<b>Dosage Form</b>	For Injectable Suspension
<b>Strength</b>	7.5 mg, 22.5 mg, 30 mg, and 45 mg
<b>Dose and Frequency</b>	7.5 mg subcutaneously every month, 22.5 mg subcutaneously every 3 months, 30 mg subcutaneously every 4 months, or 45 mg subcutaneously every 6 months
<b>How Supplied</b>	Single use kit of a two syringe-mixing system
<b>Storage</b>	Store at 2°C - 8 °C (35.6°F – 46.4 °F)
<b>Container Closure</b>	Two thermoformed trays

## **APPENDIX B. PREVIOUS DMEPA REVIEWS**

### **B.1 Methods**

On October 7, 2015, we searched the L:drive and AIMS using the terms, Eligard to identify reviews previously performed by DMEPA.

### **B.2 Results**

Our search identified 2 previous reviews<sup>1,2</sup>, and we confirmed our previous recommendations were implemented.

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<sup>1</sup> Townsend, O. Label and Labeling Review for Eligard (Leuprolide Acetate) NDA 021343/S-029, NDA 021379/S-029, NDA 021488/S-026, NDA 021731/S-026. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 APR 9. RCM No.: 2014-548.

<sup>2</sup> Harper-Velazquez, T. Labeling Review for Eligard (Leuprolide Acetate) NDA 21488. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2003 Feb 7. RCM No.: 2002-0131.

## **APPENDIX D. ISMP NEWSLETTERS**

### **D.1 Methods**

On October 7, 2015, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

<b>ISMP Newsletters Search Strategy</b>	
<b>ISMP Newsletter(s)</b>	Acute Care, Community
<b>Search Strategy and Terms</b>	Match Exact Word or Phrase: Eligard

### **D.2 Results**

The search retrieved no articles.

## **APPENDIX G. LABELS AND LABELING**

### **G.1 List of Labels and Labeling Reviewed**

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>3</sup> along with postmarket medication error data, we reviewed the following Eligard labels and labeling submitted by Tolmar on September 23, 2015.

- Prescribing Information

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<sup>3</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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TINGTING N GAO  
10/23/2015

CHI-MING TU  
10/23/2015

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 21343/S33**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

**From:** [Venugopal.Rajesh](mailto:Venugopal.Rajesh)  
**To:** [mryder@tolmar.com](mailto:mryder@tolmar.com)  
**Subject:** Eligard Labeling Supplements  
**Date:** Wednesday, January 20, 2016 2:03:09 PM  
**Attachments:** [annotated-proposed-pi-word.doc](#)

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Hello Michelle,

Attached please find our edits and comments based on our review of the PI for the following NDA and their supplements:

NDA 021343/S-033

NDA 021379/S-033

NDA 021488/S-030

NDA 021731/S-029

Should you have any questions please let me know. Otherwise, please make changes accordingly and return with a final Clean version of the attached document with a revised date of 02/2016 by 3 PM EST Friday January 29, if not sooner.

Thank you,  
rajesh

*Rajesh Venugopal, MPH, MBA  
Senior Regulatory Health Project Manager  
Division of Oncology Products 1  
Office of Hematology and Oncology Products  
OND/CDER/FDA  
Bldg. 22, Rm. 2171  
E-mail: [Rajesh.Venugopal@fda.hhs.gov](mailto:Rajesh.Venugopal@fda.hhs.gov)  
Phone: (301) 796-4730  
Fax: (301) 796-9845*

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RAJESH VENUGOPAL  
01/20/2016



NDA 021343/S-033  
NDA 021379/S-033  
NDA 021488/S-030  
NDA 021731/S-029

**ACKNOWLEDGMENT --  
PRIOR APPROVAL SUPPLEMENT**

TOLMAR Therapeutics, Inc.  
Attention: Michelle R. Ryder  
Vice President, Regulatory Affairs  
701 Centre Avenue  
Fort Collins, CO 80526

Dear Ms. Ryder:

We have received your supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

**NDA NUMBERS:** 021343, 021379, 021488, 021731

**SUPPLEMENT NUMBERS:** 033, 033, 030, 029

**PRODUCT NAME:** Eligard<sup>®</sup> (leuprolide acetate for injectable solution)  
7.5 mg, 22.5 mg, 30 mg, and 45 mg

**DATE OF SUBMISSION:** September 23, 2015

**DATE OF RECEIPT:** September 23, 2015

This supplemental application proposes the following change(s):

1. Revisions to the label to add room temperature storage information in Section 2 (Dosage and Administration) and in subsection 16.2 (Storage) to allow for flexibility when prescribing, preparing and administering the product to the patient.
2. Revisions throughout the package insert to provide further clarification of the Eligard<sup>®</sup> package insert.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 20, 2015, in accordance with 21 CFR 314.101(a)

If the application is filed, the goal date will be March 23, 2016.

NDA 021343/S-033  
NDA 021379/S-033  
NDA 021488/S-030  
NDA 021731/S-029  
Page 2

## **SUBMISSION REQUIREMENTS**

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Oncology Products 1  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have questions, call me at (301) 796-4730.

Sincerely,

*{See appended electronic signature page}*

Rajesh Venugopal, MPH, MBA  
Senior Regulatory Project Manager  
Division of Oncology Products 1  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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RAJESH VENUGOPAL  
10/02/2015

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>		
TO (Division/Office): <b>Mail: OSE</b>		FROM: Rajesh Venugopal		
DATE October 1, 2015	IND NO.	NDA NOS. 21343, 21488, 21379, 21731	TYPE OF DOCUMENT Labeling Supplement	DATE OF DOCUMENT September 23, 2015
NAME OF DRUG: Eligard	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE January 5, 2016
NAME OF FIRM:				
<b>REASON FOR REQUEST</b>				
<b>I. GENERAL</b>				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input checked="" type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):				
<b>II. BIOMETRICS</b>				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
<b>III. BIOPHARMACEUTICS</b>				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
<b>IV. DRUG EXPERIENCE</b>				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
<b>V. SCIENTIFIC INVESTIGATIONS</b>				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
<b>COMMENTS/SPECIAL INSTRUCTIONS:</b> Labeling supplements have come in for Eligard (NDAs 21343 – S33, 21488 – S30, 21379 – S33, 21731 – S29) requesting the same changes in each of the labels. The link to the submission for each NDA supplement is as follows:  <a href="#">\\CDSESUB1\evsprod\NDA021343\0051</a>  <a href="#">\\CDSESUB1\evsprod\NDA021488\0050</a>  <a href="#">\\CDSESUB1\evsprod\NDA021731\0059</a>  <a href="#">\\CDSESUB1\evsprod\NDA021379\0062</a>  The clinical team took at the supplements and has asked for a DMEPA consult to review the changes in the administration. The 6 month goal date is 3/23/16.				
SIGNATURE OF REQUESTER Rajesh Venugopal		METHOD OF DELIVERY (Check all that apply) <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> DARRTS <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

06/18/2013

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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RAJESH VENUGOPAL  
10/01/2015