threshold of ≤20 ng/dL for at least two consecutive timepoints approximately one week apart. Table 3.

Table 3. Measures of Testosterone Suppression –Intent-to-Treat Population

	Study Day									
Testosterone Suppression Measure	**Day 14 N=117**	**Day 21 N=117**	**Day 28 N=117**	**Day 35 N=117**	**Day 42 N=117**	**Day 49 N=117**	**Day 56 N=117**	**M3 (Day 84) N=117**	**Day 140 N=117**	**M6 (Day 168) N=117**
(≤ 50 ng/dL)	23 (20%)	99 (85%)	115 (98%)	116 (99%)	116 (99%)	115 (98%)	115 (98%)	115 (98%)	116 (99%)	116 (99%)
Breakthrough above 50 ng/dL	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (<1%)	1 (<1%)	1 (<1%)	0 (0%)	0 (0%)
≤ 20 ng/dL	5 (4%)	42 (36%)	98 (84%)	106 (91%)	108 (92%)	109 (93%)	106 (91%)	107 (91%)	113 (97%)	109 (93%)

For the observed-cases population, by Month 1 (Day 28) 115 of the 117 (98%) patients remaining in the study had achieved castrate T suppression, increasing to 116 patients(99%) by Day 35. Again, the remaining patient (#1801) received less than half his scheduled dose at Baseline and never achieved medical castrate T suppression. A high proportion of patients (84% at Day 28, 92% at Day 42) achieved the more stringent criteria of T suppression using a threshold of ≤20 ng/dL for at least two consecutive timepoints approximately one week apart. At the end of the study 104 of 111 (94%) patients were at or below this more stringent level.

Table 4. Measures of Testosterone Suppression – Observed Cases Population

	Study Day								
Testosterone Suppression Measure	**Day 14 N=117**	**Day 21 N=117**	**Day 28 N=117**	**Day 35 N=117**	**Day 42 N=117**	**Day 56 N=117**	**M3 (Day 84) N=113**	**Day 140 N=112**	**M6 (Day 168) N=111**
≤ 50 ng/dL	23 (20%)	99 (85%)	115 (98%)	116 (99%)	116 (99%)	115 (98%)	112 (99%)	112 (100%)	111 (100%)
Breakthrough above 50 ng/dL	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (<1%)	1 (<1%)	0 (0%)	0 (0%)
≤ 20 ng/dL	5 (4%)	42 (36%)	98 (84%)	106 (91%)	108 (92%)	106 (91%)	104 (92%)	109 (97%)	104 (94%)

8.6.5 Maintainence of castrate T levels

All patients who achieved castrate T suppression (50 ng/dL) remained suppressed throughout their participation in the study, with the exception of one patient (#1701). This patient achieved castrate suppression at Day 21 and later

experienced a breakthrough at Day 49 (T 112 ng/dL). His T continued to rise until it reached a high of 557 ng/dL at Day 85, one day after his second injection. His T then declined until Day 98, when it was 27.0 ng/dL. His T levels then remained ≤50 ng/dL throughout the remainder of the study. The median time to castrate suppression was 21 days while the mean time to castrate suppression was 21.9 days. In addition, no acute-on chronic responses were observed in any patients following any of the post-Baseline study injections.

8.6.6 Acute increases in serum T levels following repeat dosing

Acute-on-chronic responses were not observed in this study.

Medical officer's comments:

1. A superactive GnRH agonist has the potential to increase serum testosterone concentrations on repeat dosing, even in the face of apparent prior suppression of testosterone. Such increases may be of a source of clinical flare phenomenon. This study did not demonstrate this phenomenon.

2. The pharmacodynamic effects of ELIGARD™ effects are similar to those reported following long-term administration of other superactive GnRH agonists.

3. These efficacy results support the sponsor's contention that the pre-defined efficacy end-points were achieved.

8.6.7 Overall changes in T concentrations

The mean Testosterone concentration at Baseline was 367.1 — ng/dL, with the middle 50% of the data ranging from — ng/dL. Concentrations increased until a maximum mean concentration of 588.0 — ng/dL was reached on Day 2. By Day 14, the mean concentration (99.4 ±5.8 ng/dL) was below the mean Baseline concentration and by Day 21 the mean concentration (31.4 ±2.3 ng/dL) was below the medical castrate threshold. By Day 28, the mean concentration (15.2 ±1.4 ng/dL) was well below 20 ng/dL. Mean concentrations remained well below the 50 ng/dL castrate threshold, but increased transiently and minimally following the second injection from 8.3 ±0.5 ng/dL at Month 3 (Day 84: hour 8) to a mean concentration of 16.3 ±4.6 ng/dL on Day 87, and then decreased consistently throughout the following month. By Month 6 (Day 168), mean T concentrations averaged 10.1 ±0.7 ng/dL. Results were similar across centers(Figure1).

Medical officer's comment:

Review of data-sets submitted affirmed the T profile outlined above by the sponsor.

Secondary efficacy variables

8.6.8 Changes in serum LH concentrations

The mean LH concentration at Baseline was 9.2 [redacted] MIU/mL, with the middle 50% of the data ranging from [redacted] MIU/mL. Concentrations increased until a maximum mean concentration of 43.1 [redacted] MIU/mL was reached at Hour 8 post-Baseline. By Day 7, the mean concentration (8.5 MIU/mL) had decreased below the Baseline concentration, and concentrations then dropped consistently through the first nine weeks. A straight line interpolation of the mean data (using Days 21, 28, 35, and 42) suggest that the 1 MIU/mL threshold was crossed by Day 23. Concentrations increased slightly to 0.5 MIU/mL at Day 85 following the Month 3 (Day 84)injection and then decreased steadily throughout the following three weeks and at Month 6 the mean LH concentration was less than 0.1 MIU/mL.

8.6.9 Changes in serum leuprolide concentrations

A subset of 25 adult male patients with advanced prostate cancer enrolled in the pivotal Phase 3 study of LA-2550 22.5 mg was designated for the PK analysis group (Group A). Patients in the PK subset had a mean age of 73.2 years (range, 62 – 84 years, with 60% over age 70), and a mean body weight of 185.9 lbs [84.5 kg] (range, 135 – 255 lbs [61.4 – 116 kg]). Patients in this subset were identified as white (76%), black (16%), Hispanic (4%), and Asian (4%). After the first dose, serum leuprolide concentrations were measured at Hours 0 (pre-dosing), 4 and 8, and on Days 1, 2, 3, 7, 14, 21, 28, 35,
42, 49, 56, 63, 70, 77, and Month 3 (Day 84) (prior to second dose). After the second dose, serum leuprolide concentrations were measured at Hours 4 and 8, and on Days 1, 3, 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, and Month 3 (Day 84). The PK profile of leuprolide in serum after each administration of LA-2550 22.5 mg is shown in the(figure 1)

Medical officer's comments:

The pivotal study showed that ELIGARD™ 22.5 mg achieved constant suppression of testosterone secretion by maintaining serum leuprolide exposures at levels above the minimum required for complete inhibition of gonadotropic hormone release.

8.6.10 Patient performance status

At Baseline, and Days 28, 56, Month 3 (Day 84), Days 112, 140, and Month 6 (Day 168), patient performance status was evaluated using a WHO performance scale. The scale consisted of three categories, ranging from 0 to 2 with the following definitions: 0 = Fully active, able to carry on all pre-disease performance without restriction; 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; 2 = Ambulatory and capable of self-care but unable to carry out any work activities. Very little change was observed throughout the study in terms of performance status. At Baseline, 94% of patients were classified as fully active (Status = 0). By Month 6 (Day 168) this percentage increased to 96%. The percentage of patients with a score of 1 at Baseline was 6%, decreasing to 4% by Month 6 (Day 168). All patients had scores of either 0 or 1 during the study. Results were consistent across centers.

8.6.11 Patient assessments of bone pain and urinary symptoms

Bone pain, urinary pain and urinary symptoms were assessed by patient scales ranging from 1 to 10 and collected at Baseline, Days 1, 2, 3, 7, 14, 28, 56, Month 3 (Day 84), Days 85, 87, 91, 98, 112, 119, 126, 140, 147154, and Month 6 (Day 168). Pain was assessed on a scale ranging from 1 (no pain) to 10 (worst pain possible). Symptoms on urination were also assessed on a scale ranging from 1 to 10 with 1 defined as no difficulty and 10 defined as very difficult. At Baseline, patients experienced little bone pain overall, with a mean score of 1.20 and ranging from 1 to 9. This score remained low throughout the study with a mean score of 1.22 at Month 6 (Day 168), ranging from 1 to 5. Urinary pain was similarly low, with a mean of 1.02 at Baseline (range: —) and 1.10 at Month 6 (Day 168) (range: —). Likewise, urinary symptoms were low throughout the study. At Baseline, the mean symptom score was 1.09 (range: —), and 1.18 at Month 6 (Day 168) (range: —). Clinically, it is well recognized that brief symptomatic flare may occur following therapy with leuprolide acetate or other LH-RH agonists, sometimes necessitating concomitant medication or other treatment. However, there was little if any increase in the means of these symptom scores in the three days post-dosing, suggesting that there were no flare symptoms. These overall results indicate that good symptom control was maintained during the six months of the study with no symptom or pain breakthrough or acute-on-chronic response following study injections.

Medical officer's comment:

The secondary efficacy assessments demonstrate changes similar to those reported following long-term administration of other superactive GnRH agonists. This finding reflects the fact that majority of patients in this population have hormone-sensitive tumors.

8.7 Conclusions regarding demonstrated efficacy

8.7.1 Achievement of protocol defined efficacy endpoints

Over the study period, in the intent-to-treat population treated with LA-2550 22.5 mg, 99% (116/117) of patients reached castrate suppression of T concentration, defined as T concentration of ≤50 ng/dL for two consecutive timepoints approximately one week apart. By Day 28, 115 of the 117 (98%) patients remaining in the study had achieved T suppression, and by Day 35, 116 of the 117 (99%) patients had achieved this measure. The one exception (patient #1801) received less than half of the study drug dose at the Baseline injection and was withdrawn from the study because he did not achieve medical castrate T levels. The median time to castrate suppression was 21 days, and the mean time to castrate suppressio was 21.9 days.

In addition, all but one of those patients who achieved castrate T suppression (50 ng/dL) remained suppressed throughout their participation in the study. That is, only one castrate suppression breakthrough (defined as a T concentration of > 50 ng/dL after achieving suppression) was observed during the study. Following injection of LA-2550 22.5 mg, LH concentrations increased transiently through the first three days. Eight days following the Baseline injection LH levels were below Baseline values. By Day 28 they were below the 1 MIU/mL threshold. During the remainder of the study, LH concentrations were consistently below 1 MIU/mL. At Month 6 (Day 168) mean values were 0.08(±0.01) MIU/mL, with a range of —— MIU/mL.

8.7.2 Medical officer's overall assessment of efficacy

The efficacy results from pivotal Study AGL 9909 indicated that the clinical and statistical efficacy objectives of the trial were successfully met. The sponsor's study successfully achieved the principal criteria that DRUDP has used to evaluate the efficacy of superactive GnRH analogs in the palliative management of prostate cancer.

8.7.3 Support of efficacy claims in proposed label

The results of Study AGL 9909 support the sponsor's proposed label indication (the palliative treatment of advanced prostate cancer). The reviewer believes that this novel three monthly formulation of leuprolide will be another addition to the resources for the medical community in treating these patients.

9. Integrated review of safety

9.1. Data sources

The sponsor submitted safety data from the following clinical studies:

a. AGL 9904 (Eligard 7.5mg pivotal trial).
b. AGL 9802 (8 orchiectomized patients for Eligard 7.5mg)
c. AGL 9909 (pivotal Phase 3 trial for Eligard 22.5mg)

9.2. Description of patient exposure

In the study 9909, 117 patients with carcinoma of the prostate were exposed to at least a single SC injection of study drug. Of these, 113 patients received two SC injections of study drug. Six patients discontinued during the study.
Two patients voluntarily withdrew their consent from the study: one patient (#0102) discontinued at Day 71 due to transportation problems and received only one injection; the second (#2002) received two injections and discontinued at Day 134 due to an illness in the family requiring his extended absence. Two patients discontinued due to progression of disease: patient #2402 experienced increases in bone pain beginning at Day 14 following his Baseline injection. Testosterone levels were 350 ng/dL at Baseline and peaked at 600 ng/dL at Day 3. By Day 7, these values had returned to Baseline levels (362 ng/dL) and by Day 14 were well below Baseline (99 ng/dL). At Day 21 levels were below medical castrate (23 ng/dL) and remained below castrate until the patient was withdrawn (Day 64). The investigator determined the patient had experienced metastatic progression of prostate cancer and he was withdrawn from the study prior to receiving the second injection. Patient #2602, shortly after the first injection, went to ——— for a second opinion of his prostate cancer. At that time, the cancer was found to be locally recurrent, and ——— advised him to start radiotherapy. The investigator therefore discontinued him from the study at Day 78 and classified the cause as progression of disease.
One patient discontinued at Day 155 due to AEs. Patient #3401 experienced a severe shortness of breath owing to congestive heart failure and chronic obstructive pulmonary disease and was hospitalized in the last month of the study. He received two injections. Patient #1801 was withdrawn from the study at Day 74 because he did not receive a full dose of the study drug at the first injection. He consequently did not experience complete T suppression within the required time frame.

Medical officer's comment:

The number of patients exposed to the three monthly formulation of ELIGARD™ 22.5 mg, and the duration of its exposure, in conjunction with the historical information relevant to other 90-day formulations, is considered adequate to assess the general safety of ELIGARD™ for the indication of management of advanced prostate cancer.

9.3. Safety assessments conducted in the primary safety study

9.3.1. Procedures for collecting safety data

At each clinical visit, patients were assessed for potential adverse events.At each visit, adverse events were recorded on a visit-specific adverse event case report form (CRF). The severity of the adverse event was graded in accordance with the World Health Organization (WHO) toxicity scales as provided in the study protocol. Additional information about serious adverse events was provided to the sponsor on a separate serious adverse event (SAE) form.

Local tolerance to the study drug (assessed as "swelling", "redness", "bruising", "pain" and "induration") was recorded separately.

9.3.2. Analysis and reporting of safety data.

9.3.2.1. Adverse events

Adverse events were classified into body system categories. Adverse events were coded into preferred terms using the World Health Organization (WHO) Adverse Reaction Dictionary (ARD)/ECOG. Adverse events were summarized by the number of patients reporting an event and the percentage of patients with that event.

9.3.2.2. Vital signs

Vital signs including heart rate, blood pressure, respiratory rate and temperature

were documented at Screening, Baseline, and during the follow up visits.

9.3.2.3. Clinical laboratory tests

Individual laboratory values were listed by patient and by visit. Shift tables (change from baseline value to on treatment values) based on laboratory normal ranges were presented for each laboratory measurement and each assessment time. Incidence rates of new on-treatment abnormal laboratory values, based on the shift tables, were calculated and listed by laboratory test and visit. Laboratory parameters before treatment, at each visit, and the change from pretreatment values to each on-treatment assessment were presented as summary statistics

Blood samples for hematology, coagulation, and blood chemistry were collected at screening and at all visits through Month 6 for all patients. The specific assessments were:

a. Hematology: hemoglobin, red blood cell count, and total leukocytes
b. Coagulation: prothrombin time

c. Blood chemistry: Glucose, BUN, Creatinine, SGOT/AST, SGPT/ALT, alkaline phosphatase, and bilirubin.

Medical officer's comment:
Safety assessments listed are adequate for this product.

9.4. Demographics

Age, Race , Height and Weight :

The mean age of the 117 patients enrolled in the study was 73.1 years (8.0), ranging from 46–85 years. The largest majority (44.4%) of patients were 70-79 years of age, while 27% were in the 80-85 age group, 23% were in the 60-69 age group, 5% were in the 50- 59 age group, and 1% were in the 40-49 age group. Eighty percent (80%) of patients were white, 11% were black, 6% were Hispanic, and 3% were Asian. The mean height of patients was 68.2 (2.8) inches (5'8") and ranged from 55 to 74 inches. The mean weight of patients was 186 (34.8) pounds, ranging from 130-296 pounds. Demographics were similar across centers.

Medical Conditions:

Seventy-two percent (84/117) of patients enrolled in the study reported a history of urinary/renal conditions. In addition, 69% (81/117) reported a history of musculoskeletal conditions, 62% (73/117) reported a history of gastrointestinal and head, eyes, ears, nose, and throat (HEENT) conditions, 57% (67/117) reported endocrine or metabolic conditions, 44% (52/117) reported allergies, 40% (47/117) reported reproductive conditions, 36% (42/117) reported psychiatric or neurotic conditions, 32% (37/117) reported dermatologic or connective tissue conditions, 23% (27/117) reported respiratory conditions, 17% (20/117) reported hematopoietic or lymphatic conditions, 13% (15/117) reported infectious diseases, and 11% (13/117) reported hepatic conditions. Less than 10% of patients reported conditions in the following systems listed in descending order of frequency: drug/alcohol abuse and general body.

9.5. Adverse events

9.5.1. Overview of adverse events

There were no deaths reported. One hundred seventeen men with carcinoma of the prostate received at least one SC injection of LA-2550 22.5 mg. The majority

of patients were white, older males in their seventies, 2% were classified as Jewett stage A, 16% were classified as Jewett stage B, 51% were classified as Jewett stage C, and 31% were classified as stage D. Over 70% had a history of urinary tract symptoms at Baseline.

There were no clinically significant changes observed in vital sign measurements (temperature, heart rate, blood pressure and respiratory rate) during the clinical trial. A reduction was noted in the incidence of patients with abnormal prostate findings on physical examination over the study from 96 of 117 (82%) patients at Baseline to 76 of 117 patients (65%) at Month 6.

One patient was prematurely discontinued from the study due to an adverse event (AE). No IND safety reports were filed. One SAE was reported during the Screening phase, before study drug administration. Post Baseline, there was a total of 14 serious AEs reported for 12 patients. None was considered related to study drug.

Overall, there were 808 all-causalities AE's, of which 789 (98%) were mild to moderate in severity. Nineteen all-causalities AE's were classified as severe by the Investigator. Two hundred forty eight (248) treatment-related AE's were reported by a total of 96 participants. Of the 248 treatment-related events, 206 (83%) were reported as mild and only two were reported as severe. These latter two events were bladder spasms and difficulty urinating. The most common AE's found in the treatment- related categories were: hot flashes, fatigue/lethargy/weakness, urinary frequency, testicular atrophy/pain, arthralgia, stinging, burning, erythema, bruising and pruritus at the site of administration.

No injection site AE's were reported following the majority of study drug injections. Localized AE's were reported for a minority of injections. Injection site AE's were very brief in duration, mild in intensity, and sporadic in nature. Injection site AEs did not provoke clinical concern. No patients discontinued the study due to these events. No patients discontinued the study due to these events. Local injection site reactions are discussed specifically in Section 8.2.3 under the subheading, Localized Injection Site Adverse Events).

Other AEs noted e.g., hot flashes, testicular atrophy etc. were those typically associated with T suppression and consequent upon medical castration.

There were no clinically significant changes observed in vital sign measurements (temperature, heart rate, blood pressure and respiratory rate)

9.5.2. Deaths

There were no deaths reported in NDA 21-379.

9.5.3. Serious adverse events

One SAE was reported during the Screening phase, before study drug administration. Post Baseline, there was a total of 14 serious AEs reported for 12 patients. None was considered related to study drug.
Of the 14 SAE's that occurred post study drug administration, twelve were defined as serious by the hospitalization criterion and two were defined as serious by the significant medical hazard criterion. None of these 14 events was considered to be related to treatment with LA-2550 22.5 mg by the Investigator. Only one patient (#3401) was prematurely discontinued because of a SAE. No patients were prematurely discontinued owing to non-SAE's.

SAE's occurring in the interval between Screening visit and Baseline

Patient [redacted] was a 63 year old male with a previous medical history of myocardial infarction/99 and stent of right circumflex artery/99, hypercholesterolemia/93, and hypertension/85. The Screening visit took place on 9/13/00 and his concomitant medications at this time included: Baycol, Z beta, aspirin, and Norvasc. Resting EKG on 9/15/00 showed normal sinus rhythm with non-diagnostic inferior Q-waves and minor non-diagnostic ST elevation, leads 1 and AVL. There had been no significant changes from a prior EKG taken on 7/13/00. The patient had not received any injections of LA-2550 22.5 mg when, on 9/19/00, he complained of mild chest pain lasting 2 hours. He was admitted to hospital for cardiac catheterization, at which time a stent was placed in the right coronary artery. This event was considered unrelated to study drug treatment. This patient was not enrolled into the study and thus did not receive study drug following the AE.

SAE's occurring post Baseline

Seven cardiovascular SAEs requiring hospitalization were reported for six patients.

Patient #0403 was an 80 year old male with a past medical history of hypertension /94, myocardial infarction /94, arrhythmias /94, angina /92, carotid atherectomy twice /92/94, hypercholesterolemia /94, and chronic lymphocytic leukemia (stage 0) /80, gastroesophageal reflux disease/74, peripheral neuropathy /97. Concomitant medications at study entry included: isosorbide, aspirin, Norvasc, Hyzaar, Niaspan, Iberet folic and Cipro. The patient received the first and second injections of LA-2550 22.5 mg on 8/22/00 and 11/14/00, respectively. He was diagnosed with congestive heart failure on 1/3/01, and on 1/10/01 (57 days after the 2nd injection), and presented in the emergency room complaining of increasing shortness of breath, swelling and weight increase of over 30 pounds during the previous two months. An acute exacerbation of the previously diagnosed congestive heart failure was diagnosed and the patient was

admitted to the intensive care unit for workup and treatment. The patient was discharged in good condition on 1/24/01 with the additional medications of Teveten, potassium, Levaquin, Nitrol patch, carvedilol, aldactone and Lotensin. This event was considered unrelated to study treatment.

Patient #1601 was a 72 year old male with a medical history of gout /71, myocardial infarction /78, coronary artery bypass graft /79, hypertension /94 and angioplasty three times in the last 8 years. On study entry, concomitant medications included metoprolol, Hytrin, colchicine, Zyloprim and aspirin. The patient received the first injection of LA-2550 22.5 mg on 7/18/00. On 9/20/00 (35 days after the initial injection), he was routinely admitted to hospital for a scheduled workup of his intermittent bradycardia. The patient had complained of episodes of lightheadedness or angina related to slow pulse rate for the prior month. During his admission, he complained of an episode of chest pain and some brief postural hypotension. Investigations showed sinus node dysfunction with junctional arrhythmia and bifascicular block and a permanent pacemaker was implanted on 9/22/00. Recovery was uneventful and the patient was discharged on 9/24/00. This event was considered unrelated to study drug treatment.

Patient #2004 was a 75 year old male with a history of gout /75, anemia /96, hypercholesterolemia /80, chronic renal insufficiency /90, cardiac infarction /77, angina /97, hypertension /97, angioplasty /77, coronary artery bypass graft /98 and arrythmias /98. On entry to the study his medications included: lanoxin, allopurinol, aspirin, captopril, metoprolol, folic acid and iron. He received the first injection of LA-2550 22.5 mg on 8/22/00 and the second injection on 11/14/00. On 10/13/00 (41 days after the initial injection), he was hospitalized overnight for a cardiac catheterization to evaluate his coronary arter disease after an 11-day history of worsening symptoms and an abnormal EKG. The procedure and recovery were uneventful and he was discharged on 10/14/00.
A second SAE was reported for this patient. On 11/14/00 (the day of the second injection of study drug), several hours after his study injection, while having blood drawn, he experienced a two minute vasovagal episode with a drop in blood pressure and was admitted to the emergency room for evaluation. He was not admitted to the hospital, but was discharged from the emergency room after evaluation. Both events were unrelated to study treatment.

Patient #2614 was a 77 year old male with a medical history of hypertension /65, heart murmur/48, and edema/96. Concomitant medications upon entry to the study included: spironolactone, Adalat, Lotensin, K-tab, and Hyoscyamine. The patient received one injection of LA-2550 22.5 mg on 11/6/00. On 12/23/00 (47 days after the initial injection), he had a syncopal episode and fell which resulted in a fracture of the left fibula. He was admitted for diagnostic workup of the syncope. Cardiac investigations revealed worsening hypertension and that he had 5% reversible perfusion defect in the inferior lateral wall upon cardiac stress

testing and diastolic dysfunction on echocardiogram indicative of heart failure. He was discharged on 12/30/00 with the following additional medications: aspirin, lisinopril and nitroglycerin. This event was considered unrelated to study drug treatment.

Patient #2615 was a 76 year old male with a medical history of hypertension /54, non-insulin dependent diabetes mellitus/00 and hypercholesterolemia /00. Concomitant medication on study entry ncluded: Avandia, captopril, doxazosin, and simvastatin. The patient eceived the first and second injections of LA-2550 22.5 mg on 1/6/00 and 1/29/01, respectively. On 2/26/01 (28 days after the 2nd injection), the patient noticed lethargy and a slow heart rate upon awakening. An EKG performed in his physician's office showed a moderate bradycardia with AV block. He was admitted for observation on 2/26/01, atenolol was discontinued, and Norvasc was administered for hypertension. The patient was discharged on 2/28/01. This event was considered unrelated to study drug treatment.

Patient #2616 was a 78 year old male with a past medical history of angina /90 and two cardiac bypass grafts /90. Concomitant medication on entry to the study included: Zocor, Diclofenac and Flovax. The patient received the first and second injections of LA-2550 22.5 mg on 11/7/00 and 1/30/01, respectively. On 4/9/01 (65 days after the 2nd injection), he was admitted overnight for routine coronary artery catheterization to investigate the status of bypass grafts and other cardiac vessels. The catheterization was scheduled because the patient had complained of an increase in fatigue and shortness of breath upon exertion (3/27/01), and T wave inversions were then noted on an electrocardiogram (4/9/01). During the catheterization, a stent was placed in the circumflex artery. Recovery was uneventful and the patient was discharged on 4/10/01. This event was considered unrelated to study treatment. Two digestive System SAEs requiring hospitalization were reported for two patients.

Patient #0904 was an 83 year old male with a two year history of left inguinal hernia. On entry to the study he was taking multivitamins and aspirin only. He received the first and second injections of LA-2550 22.5 mg on 9/25/00 and 12/18/00, respectively. On 2/17/00 (62 days after the 2nd injection), he presented to the emergency room complaining of severe pain in the left lower abdomen which had started about one week earlier. Upon examination, he was found to have an incarcerated inguinal hernia. He was admitted. The hernia was reduced and surgically repaired on 2/18/00. The patient recovered uneventfully and was discharged on 2/20/01. This event was considered unrelated to study drug treatment.

Patient #2008 was an 81 year old male with a past medical history of deep vein thrombosis /45, appendectomy /37,cholecystectomy /90, cutaneous lupus /96, hyperthyroidism treated with radioactive iodine in /98, hypertension for the previous 30 years, and an 18 month history of abdominal hernia. His

medications atScreening included:hydrochlorthiazide, K-dur, hydroxychloroquine, and fluocinonide cream. The patient received the first and second injections of LA 2550 on 11/14/00 and 2/6/01, respectively. On 4/2/01 (55 days after the 2nd injection), the patient started vomiting and presented to primary care physician on 4/3/01 where he was prescribed compazine and returned home. The vomiting continued and he returned to primary care physician on 4/4/01 and was sent to the emergency room whence he was admitted to hospital with a diagnosis of incarcerated abdominal hernia. Surgical repair of the hernia occurred on 4/5/01 and although complaining of fatigue and weakness, the patient made an uneventful recovery. The patient was discharged on 4/8/01. This event was considered unrelated to study drug treatment.

Two respiratory System SAEs requiring hospitalization were reported for two patients.

Patient #2801 was a 70 year old male with a previous medical history of MI /90, hypertension /84, colonic polyps /89 and an episode of acute bronchitis /90. On admission to the study his concomitant medications included; lisinopril and felodipine. He received the first and second injections of LA-2550 22.5 mg on 10/16/00 and 1/8/01, respectively. On 1/23/01 (16 days after the 2nd injection), the patient presented at the emergency room complaining of a cold with nasal congestion, cough and progressive shortness of breath starting on 1/16/01. He was placed in an observation bed and given steroids, antibiotic and nebulized bronchodilators. He was admitted to hospital on 1/24/01, because his symptoms had not completely resolved and he had no previous history of chronic lung disorders, smoking or allergies. Therapy with nebulized bronchodilators, antibiotics and steroids were continued, felodipine was stopped and valsartan substituted. Upon admission he was found to have normal eosinophil absolute counts but elevated absolute and percentage neutrophil counts, which normalized over the course of his stay. Echocardiogram (normal LV size, Functional EF 60%, mild MR, mild LAE, pulmonary pressure 36 mmHg) and pulmonary function tests (FVC 77%, FEV1 77%) were performed and a diagnosis of hyperreactive airways with unknown etiology was made. On 1/27/01, the patient was discharged in stable condition with additional medications of albuterol, Azmacort and Atrovent inhalers, oral prednisone, Zithromax and valsartan. This event was considered unrelated to study drug treatment.

Patient #3401 was a 78 year old male with a 20 year history of chronic obstructive airways disease and emphysema secondary to smoking, previous spontaneous left Pneumothorax, and partial left upper lobar resection for bullous emphysema /66, coronary artery bypass graft /85 and /89, repair of abdominal aortic aneurysm /86 and glaucoma /98. Concomitant medications on entering the study included Theodur, aspirin, Xalatan, Azopt and supplemental oxygen. He received the first and second injections of LA-2550 22.5 mg on 10/30/00 and 1/22/01,respectively. On 4/8/01 (76 days after the 2nd injection), he was admitted

to hospital after complaining of severe difficulty breathing upon exertion, orthopnea and paroxysmal nocturnal dyspnea. This followed a three-week history of increasing shortness of breath, for which he had been given oral and nebulized albuterol, oral prednisone and Keflex. Upon admission to hospital he was noted to have a supraventricular tachycardia (intermittent atrial fibrillation and flutter) and pulmonary infiltrates indicative of congestive heart failure. An echocardiogram showed an ejection fraction of 40%. He was given a diagnosis of mild CHF secondary to severe chronic obstructive pulmonary disease and treated with fluid restriction, albuterol, Cardizem, Lasix, digoxin, prednisone, Altace, and amiodarone. The patient improved significantly and was discharged home on 4/12/01with the additional medications of oral prednisone, Azmacort, Atrovent, potassium, Altace, digoxin, aspirin, and Cordarone. This event was considered unrelated to study drug treatment. The patient discontinued the study due to the SAE. The date of discontinuation was retrospectively documented as 4/2/01 (Day 154 visit), because the patient was hospitalized at the time of the Day 161 and Month 6 (Day 168) study visits, and upon discharge from hospital, the patient did not feel well enough to return for a study exit visit.

Two neoplasm (benign and malignant) SAEs were reported for two patients.
Patient #1802 was a 76-year-old male who received one injection of LA-2550 22.5 mg on 7/24/00. On 10/3/00, he was hospitalized overnight for excision of the right parotid gland. The patient had a two-month history of a mass in his right cheek, which fluctuated in size. Previous biopsy on 8/15/00 had shown that the mass was a benign parotid adenoma. On 10/30/00, he developed an infection at the site of excision, which was described as an abscess. He was prescribed Keflex for this. The inflammation resolved over 18 days. This event was considered unrelated to study drug treatment.

Patient #1903 was a 75-year-old male who noticed some areas of dry skin on his back in July 2000. At the Screening visit, 8/30/00, he was noted to have patches of dry discolored skin on his back and directed to visit a dermatologist. He received an injection of LA-2550 22.5 mg on 9/25/00. On 10/13/00 (18 days after the initial injection), a dermatologist performed a biopsy of one area of skin which was reported as nodular malignant melanoma (Clark's level III). Further biopsy (November 2000) showed that the excision was complete. This event was considered unrelated to study drug treatment.

Medical officer's comment:
The reviewer agrees that none of these SAEs appeared to be related to treatment with ELIGARD 22.5 mg.

9.5.4. Premature discontinuations due to adverse events

One patient was prematurely discontinued from the study due to an adverse event (#3401, Page 28). No IND safety reports were filed.

9.5.5 Reported Adverse Events

9.5.5.1 All-causality adverse events

The majority of AE's that occurred were classified under Vascular disorders with 72 patients (61.5%) reporting events in this category. Sixty-six patients (56.4%) reported hot flashes ("Hot flushes NOS"), hypertension not otherwise specified (NOS) was reported by 5 patients (4.3%), and aggravated hypertension was reported by 3 patients (2.6%). All other events were reported by no more than two patients.

The system organ class with the second highest incidence of events was General disorders and administration site conditions, in which 71 patients (60.7%) reported events. Local site reactions included injection site paraesthesia (tingling, stinging) reported by 25 patients (21.4%), injection site burning reported by 24 patients (20.5%), injection site pain reported by eight patients (6.8%) and injection site bruising reported by four patients (3.4%). The large majority of these events were reported as mild, transient (one minute or less) in duration, and not recurrent upon subsequent injections. Fifteen patients (12.8%) reported fatigue, and eight patients (6.8%) reported weakness. Chest pain and rigors were each experienced by five patients (4.3%), and groin pain and pyrexia were experienced by four patients (3.4%) each. Three patients (2.6%) reported peripheral edema. All other events were experienced by no more than two patients.

Fifty-one patients (43.6%) reported events in the Infections and infestations system organ class. Nasopharyngitis was reported by 25 patients (21.4%), and urinary tract infection NOS was experienced by 12 patients (10.3%). Four patients (3.4%) reported influenza, and three patients (2.6%) reported upper respiratory tract infections NOS. All other events in this category were reported by no more than two patients.

In the Renal and urinary disorders system organ class, 41 patients reported events (35.0%). Ten patients (8.5%) reported dysuria, nine patients (7.7%) reported haematuria, seven patients (6.0%) each reported nocturia and urinary frequency, five patients (4.3%) each reported difficulty in micturition and micturition urgency, four patients (3.4%) experienced urinary retention, and three patients (2.6%) reported oliguria.All other events were reported by no more than two patients.

Musculoskeletal, connective tissue and bone disorders were reported by 38 patients (32.5%). The most common event in this category was arthralgia, reported by 20 patients (17.1%). Twelve patients (10.3%) reported limb pain, and eight patients (6.8%) experienced back pain. Three patients each (2.6%) reported myalgia or muscle cramps. All other events were reported by no more than two patients.

Nervous system disorders were experienced by 33 patients (28.2%). The most common event was headache NOS, reported by 17 patients (14.5%). Dizziness (exc vertigo)was experienced by 12 patients (10.3%), insomnia not elsewhere classified (NEC) was reported by six patients (5.1%), and hypoaesthesia was experienced by four patients (3.4%). All other events in this system organ class were experienced by no more than two patients.

Thirty patients (25.6%) reported Gastrointestinal disorders , with the most common event, nausea, reported by eight patients (6.8%). Sore throat NOS was reported by seven patients (6.0%) and constipation by six patients (5.1%). Diarrhea NOS or vomiting NOS were each reported by four patients (3.4%), and abdominal pain NOS or dyspepsia were reported by three patients (2.6%) each. All other events were reported by no more than two patients.

In the Skin and subcutaneous tissue disorders system organ class, 26 patients (22.2%) reported events. Pruritus NOS was reported by seven patients (6.0%) and four patients each (3.4%) reported contusion or dermatitis NOS. Three patients (2.6%) reported increased sweating, and all other events were reported by no more than two patients.

Twenty-three patients (19.7%) reported events in the Investigations system organ class. Four patients (3.4%) reported increased blood triglycerides, and three patients (2.6%) each reported increased blood glucose, prolonged prothrombin time or white blood cells in urine. All other events were reported by no more than two patients.

Respiratory, thoracic and mediastinal disorders were reported by 19 patients (16.2%). Five patients (4.3%) reported cough, and four (3.4%) reported rhinorrhea. Three patients each (2.6%) reported dyspnea NOS, pulmonary congestion or sinus congestion, and all other events were reported by no more than two patients. In the Reproductive system and breast disorders class, 16 patients (13.7%) experienced events. Five patients (4.3%) reported testicular pain, and 3 (2.6%) reported testicular atrophy. Remaining events were reported by no more than two patients.

Under Metabolism and nutrition disorders, 14 patients (12.0%) reported events. Five patients (4.3%) experienced hypercholesterolemia, and all other events were reported by no more than two patients. Eleven patients (9.4%) reported events in the Injury and poisoning class. Three patients (2.6%) experienced muscle injury NOS, and remaining events were reported by no more than two patients.

Cardiac disorders were experienced by 10 patients (8.5%), with all individual events experienced by no more than two patients. Psychiatric disorders were reported by nine patients (7.7%). Three patients (2.6%) reported depression NEC, and all other events were reported by no more than two patients. Neoplasms, benign and malignant (including cysts and polyps), were reported by seven patients (6.0%). Three patients (2.6%) reported basal cell carcinoma, and all other events were experienced by no more than two subjects. In the remaining categories (Eye disorders, Blood and lymphatic system disorders, Ear and labyrinth disorders, Congenital and familial/genetic disorders, Hepato-biliary

disorders and Immune System disorders), individual events were reported by no more than two patients.

Medical Officers Comments:
The all causalty adverse events profile is consistent for this class of drugs and acceptable .

9.5.5.3 Treatment-related adverse events

Vascular disorders were reported by 68 patients(58.1%),with the majority of these (66 patients, 56.4%) being hot flashes. The remaining events were reported by one patient each. Fifty patients (42.7%) reported events under General disorders and administration site conditions. Localized site reactions were most commonly reported here, including injection site burning (23 patients, 19.7%), injection site paraesthesia (stinging)(18 patients, 15.4%), injection site pain (seven patients, 6.0%), and injection site bruising (four patients, 3.4%). Seven patients (6.0%) experienced fatigue, and all other events were reported by no more than two patients.
Twelve patients reported Renal and urinary disorders, with three patients (2.6%) experiencing urinary frequency, and all other events reported by no more than two patients. Gastrointestinal disorders were reported by six patients (5.1%), with four patients (3.4%) reporting nausea. All other events were reported by no more than two patients.
In the Skin and subcutaneous tissue disorders class, six patients (5.1%) reported events. Three patients (2.6%) reported pruritus NOS and all other events were reported by one patient each. In the Musculoskeletal, connective tissue and bone disorders class, four patients (3.4%) experienced arthralgia, with remaining events experienced by one subject each. (Table5.)

Table 5: Incidence of Treatment Related Systemic Adverse EventsReported by ≥2% of Patients (n=117) Treated with LA-2550 22.5 mg for up to Six Months

Body System	Adverse Event	Number	Percent
Cardiovascular	Hot flashes/flushes*	66	56.4%
Gastrointestinal	Nausea	4	3.4%
General Disorders	Fatigue	7	6.0%
Musculoskeletal	Arthralgia	4	3.4%
Renal and Urinary	Urinary frequency	3	2.6%
Skin	Pruritis (not otherwise specified)	3	2.6%

Medical officer's comments:
Each case of pruritus (as listed in Table 5 above) was assessed individually. The reviewer finds no relationship to study drug for any of these. There were no cases of anaphylaxis or systemic allergic reaction. Hot flashes and testicular

atrophy are frequently reported adverse events following androgen withdrawal. These are well-recognized pharmacological consequences of medical castration.

Overall, the types of adverse events reported and their frequencies are not unexpected considering the study population (e.g. older men with advanced prostate cancer). Such event terms would include skeletal pain, back pain, malaise, fatigue, and testicular atrophy.

9.5.5.4 Adverse events by race, age, weight, disease stage

9.5.5.4.1. RACE

No clinically significant associations were discovered between adverse event rates and weight.

9.5.5.4.2. WEIGHT

No clinically significant associations were discovered between adverse event rates and weight.

9.5.5.4.3. DISEASE STAGE

There were also no clinically significant associations noted between adverse events and baseline disease stage by Jewett's classification system.

Medical officer's comment:

This reviewer agrees with the sponsors conclusions that the age,race and weight differences did not make significant impact on the adverse event profile of this product.

9.5.5.5 Localized injection site adverse events

9.5.5.5.4 ANALYSIS BY TOTAL NUMBER OF INJECTIONS

The majority of the injections were not associated with any reported localized AEs (SeeTable5.). The most commonly reported AE was burning on injection. This event was reported during 50 of the 230 injections (21.7% of study injections). Severity was reported as mild in 43 of 50 events (86%). This represents 19% of the total injections given in the study. Severity was reported as moderate in 7 of 230 events (3% of total study injections). No severe events were reported. Duration of the event was generally brief with 64% of all events lasting one minute or less. Of the seven reported moderate events, two of these lasted less than one minute, two lasted from one to three minutes, and three lasted five minutes or more.

Stinging at the injection site was reported after 13 of 230 injections (5.7%). Severity was reported as mild for 12 of 13 events (92%). One event was moderate, and none were severe. Events were generally brief, with 62% of all events lasting one minute or less. The one moderate event lasted between 21-40 seconds.

Pain at the injection site was reported during 8 of 230 injections (3.5% of study injections). Severity was reported as mild in 7 (88%) of eight reported events representing 3.0% of total study injections. Severity was reported as moderate in 1 (12.5%) of the eight reported events, representing 0.4% of study injections. No patient reported severe pain on injection. The subject reporting moderate pain experienced it for greater than five minutes.

Bruising was reported following four injections (1.7% of study injections). All were characterized as mild and took greater than five days to resolve. Of interest is that none of the patients on anticoagulant (warfarin) therapy at any time during the study experienced any bruising at the injection site following any of the study injections. No subject experienced more than a single bruising event.

Erythema was reported following two injections, once each in two different patients (<1% of study injections). One event was mild and the other moderate. Both events resolved in greater than five days, and neither patient experienced this event at multiple injection times. Itching was reported following one injection (0.4% of study injections). This event was categorized as mild and resolved in greater than five days.

Localized Injection Site Adverse Events by Duration

Burning on injection generally lasted for less than five minutes. Four patients (3.4%) reported duration of burning beyond five minutes – one for 15 minutes, one for 20 minutes, one for 30 minutes and one for 2 hours. Stinging at the injection site generally lasted for less than one minute. Two patients (1.7%) experienced stinging that lasted for 5 minutes. Pain at the injection site generally resolved within two days. One patient reported pain that continued for 3 days and two patients reported pain that lasted for six days. Bruising at the injection site generally lasted for more than five days, and in all patients bruising resolved within two weeks.

Localized erythema resolved in six days following injection for one patient and in 14 days for the second. The patient who reported itching at the injection site experienced this event for 7 days.

Table 6. Local Injection Site Adverse Events.

Term	Total Injections	N	% of Total
Burning	230	50	21.7
Stinging	230	13	5.7
Pain	230	8	3.5
Bruising	230	4	1.7
Erythema	230	2	0.9
Itching	230	1	0.4

Medical officer's comment:

Those localized injection site AE's, were typically mild in intensity, brief in duration and not recurrent over time. The most common injection site AE's were burning or stinging and no patient discontinued due to an injection site adverse event. Overall, local adverse event profile of this product is acceptable.

9.6 Laboratory assessments

9.6.1 Routine laboratory assessments

Mean values for hematology, clinical chemistry, and coagulation parameters were generally within normal limit ranges for all study timepoints for the study AGL 9909. No clinically significant excursions or trends were noted.

Hematology assessments included total WBC's, total RBCs, neutrophils, lymphocytes, monocytes, eosinophils, basophils, hemoglobin, hematocrit, mean cell volume, mean cell hemoglobin, and platelets.

Clinical chemistry assessments included serum glucose, blood urea nitrogen, creatinine, total protein, albumin, calcium, phosphorous, sodium, potassium, chloride, bicarbonate, triglycerides, bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, creatine kinase, and lactate dehydrogenase.

Coagulation parameters included international normalized ratio for anticoagulant monitoring, protime and partial thromboplastin time.

9.6.2. Special laboratory assessments

9.6.2.1. Prostate cancer markers

For serum PSA , there were progressive decreases in mean values over the course of the Study 9909. Mean serum PSA declined by greater than 90% over the study period.

9.6.2.2. Serum cholesterol

For serum cholesterol, mean values at Day 28 were modestly elevated over baseline. These elevations fluctuated from less than 10% over the upper normal limit.

9.6.2.3. International normalized ratio for coagulation monitoring

Mean INR values remained within normal limit range throughout the study with less than 6% increase from baseline to Month 6. The proportion of patients with very minor elevations of INR increased from one of 117 (< 1%) patients at baseline to eight of 112 (7%) at Month 6, however, the incidence of this finding at intervening timepoints varied widely. Other coagulation studies were without notable findings.

9.7. "Marked" laboratory abnormalities

Clinical laboratory safety tests were performed at centralized facilities. These facilities provided normal ranges for each analyte. Additional limits for each parameter that would indicate larger and potentially more serious deviations from normal were referred to as the "alert range". Further limits were identified for each parameter that represented substantial deviations from the normal range and were referred to as the "panic range". The sponsor defined any value in the "panic range" as "markedly abnormal".

The following values are of note:

Eleven patients had markedly abnormally elevated INR's, of whom only two were not reported to be receiving concomitant medications with anti-coagulant effects. Six patients were receiving warfarin therapy and another three patients were receiving aspirin or NSAID therapy.

Two patients had markedly low hematocrits. One patient had a markedly abnormal leukopenia associated with an absolute neutrophil count (ANC) of 360. This patient experienced an oral abcess during the trial and was treated with amoxacillin. One additional patient had an ANC of .320 which was normalized on all repeated values. One patient had a markedly abnormal increase in leukocyte number associated with his background leukemia. Two patients had markedly abnormal decreases in lymphocyte absolute counts and percentage lymphocytes. One patient had a markedly abnormal increase in percentage lymphocytes.

Medical officer's comments:

- A review of these patients' clinical outcomes revealed no irregular or outstanding clinical adverse events. Thus, while these lab values may be "markedly" elevated, they did not appear to translate into meaningful clinical adverse outcome. In addition, the incidence of such lab values was very low. Finally, these lab values might reflect the effects of other illnesses or background variables.

- Overall, all available laboratory data do not raise concerns about significant drug-induced toxicity associated with the use of the ELIGARD™ 22.5mg for the treatment of advanced prostate cancer.

9.8 Safety issues of special concern

There are no safety issues of "special concern". As a class, clinical experience has shown that superactive GnRH agonists are generally safe and well tolerated in the treatment of advanced prostate cancer.

As noted previously, prescribers must be aware of the rare potential for "clinical flare" upon initiating therapy. In addition, serious systemic allergy has been reported to occur rarely.

In the particular case of ELIGARD™ 22.5 mg , it appears that reported local site reactions were mild in severity, brief in duration, and appeared to resolve without incident. These were all within acceptable confines.

9.9 Safety consultations

No safety consultations were obtained.

9.10 Safety findings and proposed labeling

Minor changes to The ADVERSE REACTIONS section were recommended.

10. Package insert

The proposed package insert was reviewed in great detail. Overall, the PI was accurate and clear. However, some modification of the clinical information was deemed necessary. These proposed changes in the PI were forwarded to sponsor.

11. Use in special populations

Women and children were not studied for this indication (treatment of advanced prostate cancer). These groups are contraindicated in the package insert.

The pharmacokinetics of ELIGARD in patients with renal or hepatic insufficiency were not studied for this NDA. While this fact is noted in the package insert, it is not considered a safety issue because clinical experience has revealed leuprolide to be very safe even at high concentrations and because leuprolide is rapidly metabolized by enzymes that break down proteins.

12. Conclusions and recommendations

12.1. Overall risk/benefit assessment

The reader is also referred to the Executive Summary section of this review.

Benefits: Surgical castration is the standard against which hormonal therapies for the palliative management of advanced prostate cancer have been compared. The goal of

androgen suppression therapy is to reduce serum testosterone concentrations to levels comparable to those observed following orchiectomy (≤ 50 ng/dL). Superactive GnRH agonists that suppress serum testosterone to castrate levels have been shown to have comparable long-term efficacy as orchiectomy, as assessed by time to disease progression and survival.

The results of Study AGL 9909, the principal efficacy and safety study supporting this NDA indicate that the 3 month formulation of ELIGARD™ is effective in suppressing serum testosterone to ≤ 50 ng within 28 days of first dosing and in maintaining serum testosterone at ≤ 50 ng through 2 dosing cycles (168 days) in greater than 90% of patients. In addition, there was no clinically meaningful acute-on-chronic phenomenon seen during the course of the studies. These findings are considered sufficient to support the efficacy of the ELIGARD™ for the palliative treatment of advanced prostate cancer.

Risks: In contrast to surgical castration, treatment with a superactive GnRH agonist initially results in a temporary (1-2 weeks) increase in gonadal androgen secretion before reducing serum testosterone to castrate levels. The initial rise in serum testosterone may cause a temporary worsening of symptoms referred to as "a flare." Most commonly, the androgen-induced flare consists of an increase in bone pain in patients with advanced prostate cancer. Less frequently, more serious complications such as compression of the spinal cord with motor impairment can occur. This potential complication is a labeled warning for all superactive GnRH agonists. The likelihood of such serious complications is diminished with earlier diagnosis of prostate cancer, as is occurring today in the United States. The risk of a clinically serious complication resulting from the initial surge of testosterone at the onset of treatment with ELIGARD™ should be no different than that associated with the use of other presently approved superactive GnRH analogs.

Vast clinical experience had shown that GnRH agonists are safe and well tolerated for the treatment of prostate cancer. Since GnRH analogs are small peptides, they have the potential to induce antibody formation and hypersensitivity reactions. Rare reports of systemic allergic reaction have been noted in the literature.

In summary, based on safety and efficacy information submittes in NDA 21-379, this reviewer believes that ELIGARD™ is safe and effective for the proposed indication of palliative treatment of advanced prostate cancer.

12.2. Recommendations

It is recommended that the three monthly formulation of ELIGARD™ 22.5mg should be approved for the proposed indication of *" palliative treatment of advanced prostate cancer".*

Ashok Batra, MD

Medical Officer
Division of Reproductive and Urologic Drug Products
Arch NDA 21-379
cc: HFD-580/Div File
HFD-580/DShames/MHirsch/AReddy

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

/s/

Ashok Batra
6/21/02 09:46:16 AM
MEDICAL OFFICER

Mark S. Hirsch
6/30/02 03:18:36 PM
MEDICAL OFFICER
I concur.

NDA 21-379
Filing meeting : luperogel 22.5 mg-Atrix Labs Inc.
CLINICAL REVIEWER: ASHOK BATRA

DRUG:
LA-2550 22.5 mg is a sterile polymeric matrix formulation of leuprolide acetate for subcutaneous injection. It is designed to deliver 22.5 mg of leuprolide acetate at a controlled rate over a three-month therapeutic period.

Leuprolide acetate is a synthetic nonapeptide analog of naturally occurring gonadotropin releasing hormone (GnRH or LH-RH) that, when given continuously, inhibits pituitary gonadotropin secretion and suppresses testicular and ovarian steroidogenesis.

Dose: It is designed to deliver 22.5 mg of leuprolide acetate at a controlled rate over a three-month therapeutic period.
Delivery: LA-2550 22.5 mg is prefilled and supplied in two separate, sterile syringes whose contents are mixed immediately prior to administration.
The two syringes are joined and the single dose product thoroughly mixed before injection. One syringe contains the ATRIGEL® Delivery System, and the other contains lyophilized leuprolide acetate. ATRIGEL® is a polymeric (non-gelatin containing) delivery system consisting of a biodegradable, [redacted] poly (DL-lactide-co-glycolide) (PLG) polymer formulation dissolved in a biocompatible solvent, [redacted], *N*-methyl-2-pyrrolidone (NMP). PLG is a co-polymer with a 75:25 molar ratio of DL-lactide to glycolide containing carboxyl end groups. The second syringe contains lyophilized leuprolide acetate and is designed to deliver 22.5 mg of leuprolide acetate at the time of subcutaneous injection.

INDICATIONS
One Every 3 Month LEUPROGEL™ 22.5 mg is indicated for the palliative treatment of advanced prostate cancer

Proposed label
Preliminary review of label shows its organized appropriately for the claim sought. The subsections also appropriately organized.

EFFICACY: IN pivotal open label multcenter study AG 9909 , 117 patients with advanced prostate cancer were treated with at least a single injection of study drug. Of these, 113 patients received two injections of LA-2550 22.5 mg, given once every three months. Thirty-six patients had stage D disease, 60 stage C, 19 stage B and 2 stage A. This study evaluated the achievement and maintenance of castrate serum testosterone suppression over six months of therapy.
Serum testosterone was suppressed to below the castrate threshold (≤ 50 ng/dL) by Day 28 in all but one patient (99%) who received a full dose of study drug at Baseline. At Day 35, all patients (100%) who received a full dose at Baseline attained castrate testosterone suppression. Once castrate testosterone suppression was achieved, only one (<1%) patient demonstrated breakthrough (concentrations above 50 ng/dL at anytime during the study after achieving castrate levels). This patient returned to castrate levels following his second injection and remained at castrate levels throughout the study. At the conclusion of the study (Month 6), all 111 evaluable patients (100%) had testosterone concentrations below castrate levels and 94% had achieved a recently recommended threshold of ≤ 20 ng/dl

2.) Acute on chronic phenomenon was not observed .
3) 1 patient had a breakthrough in suppression. After the 1 injection that reversed following the 2nd injection

SAFETY:

1.**Local adverse events** reported after injection of LA-2550 22.5 mg were typical of those frequently associated with similar subcutaneously injected products. In all, 230 injections of LA-2550 22.5 mg were given. Transient burning was reported following 50 of 230 (21.7%) injections, with the majority (86%) of these events being reported as mild. Stinging was reported after 13 of 230 injections (5.7%) with 92% of these reported as mild. Pain was reported following 8 of 230 (3.5%) of study injections and was routinely described as brief in duration and mild in intensity.
2.In the clinical efficacy trial , the transient increase in serum testosterone concentrations was not associated with an exacerbation of disease symptoms.(Pain,urinary,obstructive)

2.Systemic AE

Table 1: Incidence (%) of Possibly or Probably Related Systemic Adverse Events Reported by ≥2% of Patients (n=117) Treated with LA-2550 22.5 mg for up to Six Months

Body System	Adverse Event	Number	Percent
Cardiovascular	Hot flashes/flushes*	66	56.4%
Gastrointestinal	Nausea	4	3.4%
General Disorders	Fatigue	7	6.0%
Musculoskeletal	Arthralgia	4	3.4%
Renal and Urinary	Urinary frequency	3	2.6%
Skin	Pruritis (not otherwise specified)	3	2.6%

3.Serious AE

- **No Deaths**
- **One patient needed a pacemaker for arrrythmia.**

4.Urogenital: Testicular soreness, impotence, decreased libido, gynecomastia, breast soreness

Summary; (FILABLE)
Preliminary review showed that the sponsors have a Reasonable pivotal study
The submission is organized adequately to lend itself to a timely review process
ADDendum: site # 19 was chosen for inspection.

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

/s/

Ashok Batra
11/26/01 08:00:15 AM
MEDICAL OFFICER

Mark S. Hirsch
11/26/01 03:55:20 PM
MEDICAL OFFICER
I concur.

NDA 21-379
Eligard™ 22.5 mg (leuprolide acetate for injectable suspension)

Safety Update Review

Please refer to the Medical Officer's review.

/S/ 7/01/02

Memorandum for the Record

Nov. 14, 2001

From: M. Welch (HFD-715)

To: NDA 21-379 (HFD-580)

Subj: Notice of Filing Status

NDA 21-379 (stamp date 26 Sept., 2001) is filable from a statistical perspective. The primary efficacy trial is an open-label, uncontrolled, observational study demonstrating testosterone suppression for palliative treatment of patients with advanced prostate cancer. A written statistical review of the study will likely be unnecessary, other than a short memorandum.

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

/s/

Mike Welch
11/15/01 03:46:41 PM
BIOMETRICS