CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER
21-379

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review
Division of Pharmaceutical Evaluation II

NDA:	**21-379**
Brand Name:	**Eligard 22.5 mg (LA-2550)**
Generic Name:	**Leuprolide Acetate 22.5 mg**
Sponsor:	**Atrix Laboratories, Inc.**
Relevant IND(s):	✓
Date of Submission:	**26-SEP-2001**
Type of Submission:	**Original NDA**
Code:	**3S**
Formulation:	**Subcutaneous**
Strength:	**22.5 mg**
Indication:	**Palliative Treatment for Advanced Prostate Cancer**
Reviewer:	**Myong-Jin Kim, Pharm.D.**
Team Leader:	**Ameeta Parekh, Ph.D.**
OCPB Division:	**DPE-II**
ORM Division:	**Reproductive & Urologic Drug Products**

1. EXECUTIVE SUMMARY

Leuprolide (L) acetate is a potent GnRH agonist used clinically as a palliative treatment for advanced prostate cancer. While single dosing with L stimulates the release of LH and FSH, repeated dosing reduces circulating levels of LH, FSH and T by decreasing or down regulating GnRH pituitary active receptors and depleting pituitary gonadotropin stores. L acts by preventing pulsatile hypothalamic stimulation of the adenohypophysis, which results in reduced gonadotropic hormone release and suppression of gonadal testosterone to levels associated with surgical castration (≤ 50 ng/dL in serum). Currently approved L are as follows: depot IM (one-month 3.75 and 7.5 mg, three-month 11.25 and 22.5 mg, four-month 30 mg), daily 1 mg SC injection, monthly 7.5 mg SC injection, and L implant designed to deliver for 12 months.

LA-2550 22.5 mg (NDA 21-379) is an injectable polymer-based, extended-release formulation of L acetate designed to deliver a nominal dose of 22.5 mg over a three-month period after SC injection. L is contained within a biodegradable (lactic and glycolic acids) and biocompatible PLG which can deliver the drug over a period of about three months.

To seek approval of the palliative treatment of advanced prostate cancer, the sponsor submitted one phase III study (AGL 9909) of LA-2550 22.5 mg, and two studies (AGL 9802, AGL 9904) related to Atrix's recently approved one-month SC formulation, Eligard® 7.5 mg (NDA 21-343).

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE-II) has reviewed NDA 21-379 submitted on September 26, 2001. The overall Human Pharmacokinetic Section is *acceptable* to OCPB. Labeling comments outlined in the labeling section of this review have been conveyed to the sponsor and they were accepted by the sponsor on July 12, 2002.

Myong-Jin Kim, Pharm.D.

RD initialed by Ameeta Parekh, Ph.D., Team Leader /S/

FT signed by Ameeta Parekh, Ph.D., Team Leader /S/

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Terms & Abbreviations

FSH.....Follicle Stimulating Hormone
GnRH.....Gonadotrophin-Releasing Hormone
IM.....Intramuscular
L.....Leuprolide
LH.....Luteinizing Hormone
M-I.....Leuprolide (5-9)-Pentapeptide
M-II.....Leuprolide (5-7)-Tripeptide
M-III.....Leuprolide (1-3)-Tripeptide
M-IV.....Leuprolide (1-2)-Dipeptide
NMP.....N-methyl-2-pyrrolidone
PD.....Pharmacodynamics
PK.....Pharmacokinetics
PLG.....Poly (DL-lactide-co-glycolide)
RIA.....Radioimmunoassay
SC.....Subcutaneous

T.....Testosterone

3. SUMMARY OF CPB FINDINGS

Atrix Laboratories' extended release three-month formulation, LA-2550 22.5 mg, consists of L acetate in the ATRIGEL® Delivery System and is administered by a different route (SC versus IM) than the currently marketed formulation.

The Human Pharmacokinetics and Bioavailability section included one clinical study of three-month formulation (AGL 9909) and two studies (AGL 9802, AGL 9904) related to Atrix's recently approved one-month SC formulation, Eligard® (NDA 21-343). Study AGL 9909 evaluated the PK and PD of L in a subset of 22 patients with advanced prostate cancer during treatment with LA-2550 22.5 mg every 3 (84 days) months for 6 months (168 days). A phase I study (AGL9802) evaluated the PK of L in 8 orchiectomized patients for 56 days after a single dose of Eligard™ 7.5 mg. A phase III study (AGL9904) evaluated the PK and PD of L in a subset of 20 patients with advanced prostate cancer during treatment with Eligard™ 7.5 mg, given monthly for 3 months.

The one-month (NDA 21-343) and three-month (NDA 21-379) formulations differ primarily in the ratio of lactide to glycolide subunits and the molecular weights of their copolymers to achieve the different drug release profiles required for one versus three month dosing intervals.

Absorption: Serum L concentrations rose rapidly after each dose (first dose C_{max}: 127±39 ng/mL at 4.6±1.6 h, second dose C_{max} 107±50 ng/mL at 4.5±1.5 h), and then fell over the several days. Based on the AUC previously reported for a single 1 mg IV injection of L acetate in adult males (126 ng hr mL^{-1}) (Sennello *et al.* J Pharm Sci 1986;75:158-60), the AUC of a 22.5 mg IV dose of L acetate would be approximately 2,835 ng hr mL^{-1}. The mean bioavailability (F) of LA-2550 22.5 mg injections was approximately 100% after both doses.

Distribution: The literature reported mean Vd_{ss} of L 26.5 ± 10.1 L following IV bolus administration to healthy male volunteers (Sennello *et al.* J Pharm Sci 1986;75:158-60). *In vitro* binding to human plasma proteins ranged from 43% to 49% (PDR 1999).

Metabolism: No drug metabolism study was conducted with LA-2550 22.5 mg. In animals, L was metabolized to the M-I, M-II, M-III, and M-IV. Within 1 hour of IM injection of L 3.75 depot, a serum M-I concentration of 0.15 ng/mL was detected, increasing to a maximum of 0.86 ng/mL after 3 hours (Ueno & Matsuo. J Chromatograph 1991;566:57-66). In a L recipient, the concentration of this metabolite in the urine reached a peak of 4.97 µg/L within 2 days, and could still be detected (1.74 ng/mL) after 29 days (Ueno & Matsuo. J Chromatograph 1991;566:57-66).

Excretion: In healthy male volunteers, a 1 mg bolus of L administered IV revealed that the mean systemic clearance was 8.34 L/h, with a terminal elimination $t_{1/2}$ of 2.9 ± 0.5 hours based on a two compartment model. Mean elimination $t_{1/2}$ and clearance were reported to be 3.6 h and 9.1 L/h, respectively, following single SC 1 mg SC injection (Sennello *et al.* J Pharm Sci 1986;75:158-60).

Intrinsic factors: NDA 21-379 does not contain population PK study/analysis. Women and pediatric subjects were not included in the clinical study. Elderly patients made up a considerable portion of the patients studied in the clinical investigation (age range, 46 to 85 years). Patients studied ranged in weight from 59 to 134 kg and included whites, blacks, and Hispanics.

Extrinsic factors:

Drug Interactions

No drug-drug interactions have been described for other preparations of L acetate which does not appear to be metabolized by Cytochrome P450 or other phase I or phase II pathways that could lead to metabolic interactions. Because L is primarily metabolized via peptidase(s) (Chriap & Sorkin Drugs & Aging 1991;1:487-509), and is less than 50 % bound in the plasma (PDR 1999), PK drug-drug interactions are unlikely to be observed with LA-2550 22.5 mg. The effect of L on CYPs is unknown.

Biopharmaceutics:

The formulation used in Study AGL-9909 is identical to the to-be-marked formulation.

LA-2550 22.5 mg is prefilled and supplied in two separate syringes, Syringes A (ATRIGEL® Delivery system containing poly polymer formulation dissolved in NMP solvent) and B (lyophilized leuprolide acetate) whose contents are mixed immediately prior to administration. The two syringes are joined and the single dose product is mixed until it is homogenous. LA-2550 22.5 mg is then administered SC where it forms a solid drug delivery depot.

4. Question-Based Review

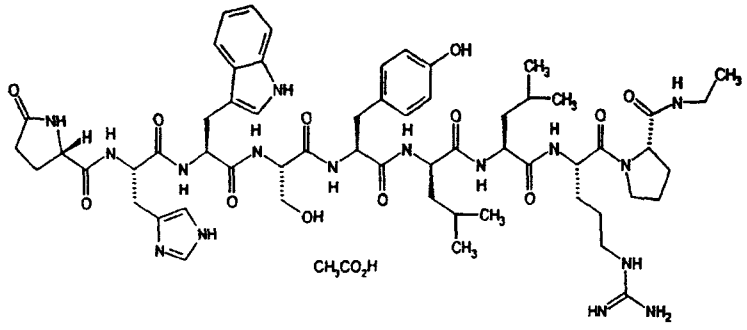
4.1 General Attributes

1. What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product?

Physico-chemical properties

L acetate is a synthetic nonapeptide analogue of the naturally occurring GnRH. Replacement of the glycine residue at the 6th position in the decapeptide by the D-isomer of leucine and attachment of an ethylamide group to the carboxyl group of proline at position 9 gives the nonapeptide.

- Structural formula:



- Molecular Weight (free acid): 1269.5 (1209.4) Daltons
- Molecular Formula: $C_{59}H_{84}N_{16}O_{12}.C_2H_4O_2$
- IUPAC name: 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate (salt)
- pK_a (histidine, tyrosine, guanidine groups): 6.0, 10.0, 13.0
- Appearance: White to off-white powder
- Solubility: Soluble in water and acetic acid
- Hygroscopicity: Hygroscopic

Formulation

LA-2550 22.5 mg is prefilled and supplied in two separate syringes, Syringes A (ATRIGEL® Delivery system containing poly polymer formulation dissolved in NMP solvent) and B (lyophilized L acetate). ATRIGEL® Delivery system consists of — 75/25 Poly (DL-lactide-co-glycolide) (PLG) and — NMP.

Summary of LA-2550 22.5 mg Clinical Lots for Study AGL 9909				
Lot No.	Dosage Formula & Strength	Batch Size	PLG Molecular Weight	Formulation or Significant Manufacturing Change
1252*	Extended release three-month depot, 22.5 mg	— —	18 kDa	None
1272	Extended release three-month depot, 22.5 mg	— —	19 kDa	None

*Twenty-two patients in the PK subset study received lot 1252 for both injections

Composition of Syringe A, ATRIGEL® Delivery System			
Component	% w/w	mg/g	mg/unit
75:25 PLG	—		
NMP	—		
Total Fill Weight: 440 mg/unit*			

*An overage of delivery system is provided due to material holdup in the syringe and needle upon injection of constituted product

Composition of Syringe B, Lyophilized Leuprolide Acetate	
Component	mg/syringe
Leuprolide acetate	28.2*

*An overage of delivery system is provided due to material holdup in the syringe and needle upon injection of constituted product

Composition of LA-2550 22.5 mg Constituted Delivery Product		
Component	% w/w	Dose delivered mg/unit
Leuprolide acetate	—	22.5
75:25 PLG	—	158.6
NMP	—	193.9
Total Delivered Amount: 375 mg/unit		

The formulations of Eligard 7.5 mg (NDA 21-343) and LA-2550 22.5 mg differ primarily in the ratio of lactide to glycolide subunits and the molecular weights of their copolymers to achieve the different drug release profiles required for one versus three month dosing intervals.

2. What is the proposed mechanism of action?

The therapeutic effects of L appear to be due to its ability to induce and maintain suppression of testicular androgen synthesis via its effects on pituitary LH release. L acts by preventing pulsatile hypothalamic stimulation of the adenohypophysis, which results in reduced gonadotropic hormone release and suppression of gonadal testosterone to levels associated with surgical castration (≤ 50 ng/dL in serum).

3. What are the proposed indication, dosage and route of administration?

LA-2550 22.5 mg SC is indicated for the palliative treatment of advanced prostate cancer.

4.2 General Clinical Pharmacology

What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (also called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

Approximately 80% of prostate cancers are dependent on circulating androgens and are responsive to hormone manipulation. Synthetic GnRH agonist, L acetate, is often used for obtaining "medical castration" by T suppression. The castrate threshold of T ≤ 50 ng/dL is used by the currently marketed formulation of L as the primary efficacy endpoint in pivotal clinical studies of GnRH agonists for the treatment of prostate cancer. In addition, T suppression ≤ 50 ng/dL provides clinical benefits equivalent to surgical castration in prostate cancer patients.

Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. The primary efficacy variable for this study was serum T concentration. Blood samples for PK analysis (serum L acetate quantitation) and T concentrations were taken at Baseline (Day 0), Hours 4 and 8 and on Days 1, 2, 3, 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77 and 84 (prior to second dose). After the second dose (Day 84), serum concentrations were measured at Hours 4 and 8 (post-dose) and on Days 1, 3, 7, 14, 21, 28, 35, 42, 49, 56, 63, 70, 77, and 84. PK parameters were calculated for each patient during the initial burst phase (0 – 3 days after dosing), and plateau phase (3 – 84 days after dosing), and over the total dosing interval.

What are the basic pharmacokinetic characteristics of L?

1. Pharmacokinetics (ADME)

a. Absorption

Serum L concentrations rose rapidly after each dose (first dose C_{max}: 127±39 ng/mL at 4.6±1.6 h, second dose C_{max} 107±50 ng/mL at 4.5±1.5 h), and then fell over the several days. Based on the AUC previously reported for a single 1 mg IV injection of L acetate in adult males (126 ng hr mL^{-1}) (Sennello *et al.* J Pharm Sci 1986;75:158-60), the AUC of a 22.5 mg IV dose of L acetate would be approximately 2,835 ng hr mL^{-1}. The mean bioavailability (F) of LA-2550 22.5 mg injections was approximately 100% after both doses and it was estimated as follows:

$F = (D_{IV}/D_{SC})\ (AUC_{SC}/AUC_{IV})$, where D is the dose and AUC the total area under the concentration vs. time curve observed for LA-2550 22.5 mg (SC) and from a previously reported study of IV L acetate (Sennello *et al.* J Pharm Sci 1986;75:158-60).

b. Distribution

The literature reported mean Vd_{ss} of L 26.5 ± 10.1 L following 1 mg IV bolus administration to healthy male volunteers (Sennello *et al.* J Pharm Sci 1986;75:158-60). The mean Vd was 33.50 ± 3.54 L using L depot (TAP 144 SR) 7.5 mg SC (Mazzei *et al* Drugs Exptl Clin Res 1989:8;373-87). In vitro binding to human plasma proteins ranged from 43% to 49% (PDR 1999).

c. Metabolism and Excretion

Metabolites of L were not measured in this study.

In animals, L was metabolized to the M-I, M-II, M-III, and M-IV. Within 1 hour of IM injection of L 3.75 depot, a serum M-I concentration of 0.15 ng/mL was detected, increasing to a maximum of 0.86 ng/mL after 3 hours (Ueno & Matsuo. J Chromatograph 1991;566:57-66). In a second L recipient, the concentration of this metabolite in the urine reached a peak of 4.97 µg/L within 2 days, and could still be detected (1.74 ng/mL) after 29 days (Ueno & Matsuo. J Chromatograph 1991;566:57-66).

No drug excretion study was conducted with LA-2550 22.5 mg SC. In healthy male volunteers, a 1 mg bolus of L administered IV revealed that the mean systemic clearance was 8.34 L/h, with a terminal elimination $t_{1/2}$ of 2.9 ± 0.5 hours based on a two compartment model (Sennello *et al.* J Pharm Sci 1986;75:158-60). The mean systemic clearances of L was 9.1 L/h with a terminal elimination $t_{1/2}$ of 3.6 h after a 1 mg SC L administration (Sennello *et al.* J Pharm Sci 1986;75:158-60).

What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

After both injections of LA-2550 22.5 mg, mean serum L concentrations peaked during the first day then fell rapidly to sustained concentrations between 0.15 – 2.40 ng/mL. In response to this characteristic of L exposure, mean serum T concentrations in the PK subset rose initially (Baseline T, 372.3 ± 164.6 ng/dL, mean ± SD), peaking at 610.6 ± 245.6 ng/dL on Day 2, then fell to below castrate levels (≤ 50 ng/dL) within 3 weeks after the first dose (27.7 ± 17.9 ng/dL on Day 21). Mean serum T remained suppressed (6.3 – 11.7 ng/dL) for the remainder of the first dosing interval (84-day). Serum T did not increase in response to the second dose of LA-2550 22.5 mg, but remained suppressed (8.7 – 13.4 ng/dL) during the entire second dose interval (84-day). The initial increase and decline in T concentrations produced by LA-2550 22.5 mg were of a magnitude and time course similar to those observed with other L formulations and are related to the mechanism by which continuous exposure to GnRH agonists suppresses gonadal steroidogenesis via hypophyseal desensitization. No acute-on-chronic or breakthrough responses in these 22 patients were seen in serum T concentrations after the second dose of LA-2550 22.5 mg.

Following injection of LA-2550 22.5 mg, LH concentrations increased transiently through the first several days (Baseline LH: 7.1 ± 4.8 MIU/mL, Day 1: 28.0 ± 15.6 MIU/mL, Day 3: 12.5 ± 5.3 MIU/mL, mean ± SD). Seven days following the Baseline injection LH levels were close to

Baseline values, 8.1 ± 4.0 MIU/mL, and by Day 14, LH concentration was 3.0 ± 1.5 MIU/mL. 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) the mean value was 0.07 ± 0.05 MIU/mL, with a range of 0.02-0.25 MIU/mL.

1. Do PK parameters change with time following chronic dosing?

Comparison of PK parameters between the first and second doses was evaluated. L concentrations during the burst phase (AUC, C_{max}) were higher after the first dose ($P < 0.05$), while concentrations during the plateau phase (AUC, C_{min}) were higher after the second dose. However, the overall AUC did not differ between the first and second doses ($P > 0.05$).

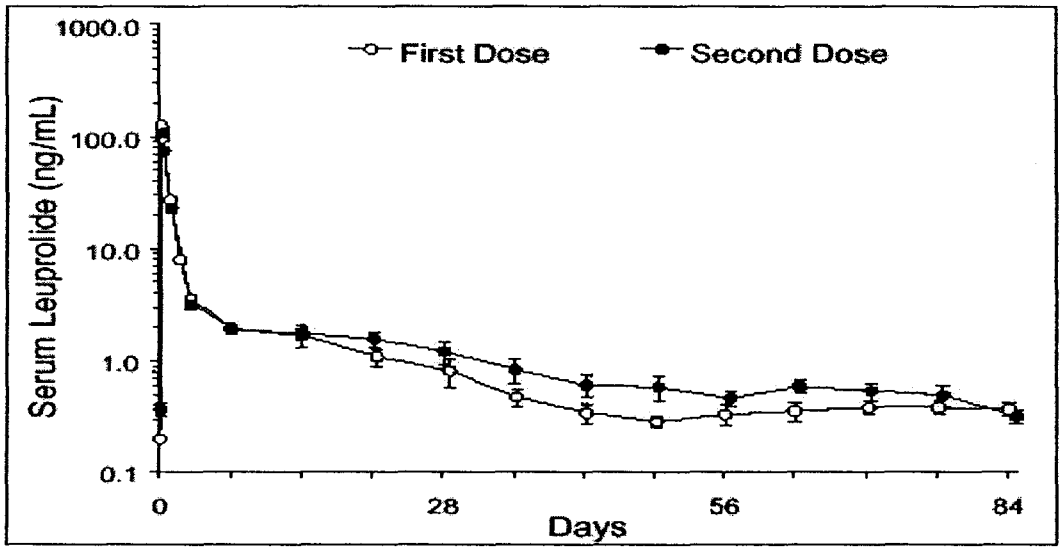
There was no evidence of significant accumulation after repeated dosing with LA-2550 22.5 mg in the Study AGL 9909. Serum L concentrations and AUC during the plateau phase following the second dose were similar to those observed after the first dose. Mean serum L concentrations at the end of the two consecutive dosing intervals were 0.34 ng/mL and 0.30 ng/mL, respectively.

Pharmacokinetic Parameters of LA-2550 22.5 mg

Dose No.	Burst Phase (0-3 days) mean±SD (range)			Plateau Phase (3-84 days) mean±SD (range)			Mean±SD (range)	
	C_{max} (ng/mL)	T_{max} (hr)	AUC (ng hr mL^{-1})	C_{max} (ng/mL)	C_{min} (ng/mL)	AUC (ng hr mL^{-1})	C_{last} (Day 84) (ng/mL)	$AUC_{(0-84d)}$ (ng hr mL^{-1})
Dose 1	126.8± 38.8	4.59± 1.59	2227	2.4	0.15	1419	0.344 ± 0.212	3645.5 ± 1100.3
Dose 2	107.1 ± 50	4.53 ± 1.5	1955	2.7	0.25	1925	0.297 ± 0.185	3880 ± 921.1

Figure 1. Comparison of Serum L Concentrations after Repeated Dosing (Study AGL 9909)

PK profile of LA-2550 22.5 mg, showing serum L levels (mean, SEM) after two consecutive SC injections at 3 month intervals in patients with advanced prostate cancer (n = 22).



2. **How long is the time to the onset and offset of the pharmacological response or clinical endpoint?**

The mean serum T concentrations in the PK subset fell below castrate levels (≤ 50 ng/dL) within three weeks after the first dose (27.7 ± 17.9 ng/dL on Day 21). The mean time to onset of T below the castration level was 19.7 days (range, Day 14 – 28).

3. **Are the dose and dosing regimen consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?**

The dose of LA-2550 22.5 mg was selected based on the dose of active drug delivered by other approved effective depot preparations of L acetate. Due to the fact that prolonged serum levels below 0.1 ng/mL may be associated with incomplete suppression of pituitary gonadotrope secretion (Tunn UW *et al* Urol Int 1998;60(suppl 1):9-17), and the wide safety margin of L acetate, the sponsor did not investigate lower doses.

4.3 Intrinsic Factors

What intrinsic factors influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?

Analyses of efficacy data by age, race, or severity of disease were not carried out.

Gender/Pediatric Patients: The indication sought is for the palliative treatment of advanced prostate cancer. Therefore, women and pediatric subjects were not included in the clinical PK studies.

Race: The clinical PK study of LA-2550 22.5 mg (AGL 9909) included white (n=19, 76%), black (n=4, 16%), Hispanic (n=1, 4%) and other (n=1, 4%). PK of L and T suppression were similar in this population.

Age: Elderly patients made up a substantial portion of the patients studied in the clinical investigation of LA-2550 22.5 mg (n=117, mean age 73.1, range 46-85, 71% over age 70). Patients in the PK subset had a mean age of 73.2 years (range, 62-84 years, with 60% over age 70).

Weight: Patients (n=25) studied ranged in weight from 61.4 to 116 kg with a mean body weight of 84.5 kg. Patients in clinical PK study received a unit dose of 22.5 mg, resulting in weight-normalized doses ranging from 194 to 366.5 μg/kg. Drug exposure varied between individual subjects, tending to be lower in patients with higher body weights ($p>0.05$). There was no evidence of significant PK variability over this range of doses, with serum L remaining at effective levels in all patients over the course of treatment.

Administration of LA-2550 22.5 mg provided sustained serum T suppression in patients whose body weights ranged from 59 to 134 kg, while maintaining mean serum levels of approximately 0.3 ng/mL at the end of each three-month dosing interval. Patients received a unit dose of 22.5 mg, resulting in weight-normalized doses ranging from 168 to 381 μg/kg.

Figure 2. Relationship of Leuprolide Exposure to Baseline Body Weight

Individual values of serum L AUC (0-84 days) are plotted against body weight for each patient in the PK analysis subset of Study AGL9909. Patients received two consecutive injections of LA-2550 22.5 mg on Day 0 and Month 3 (Day 84) (n=22).

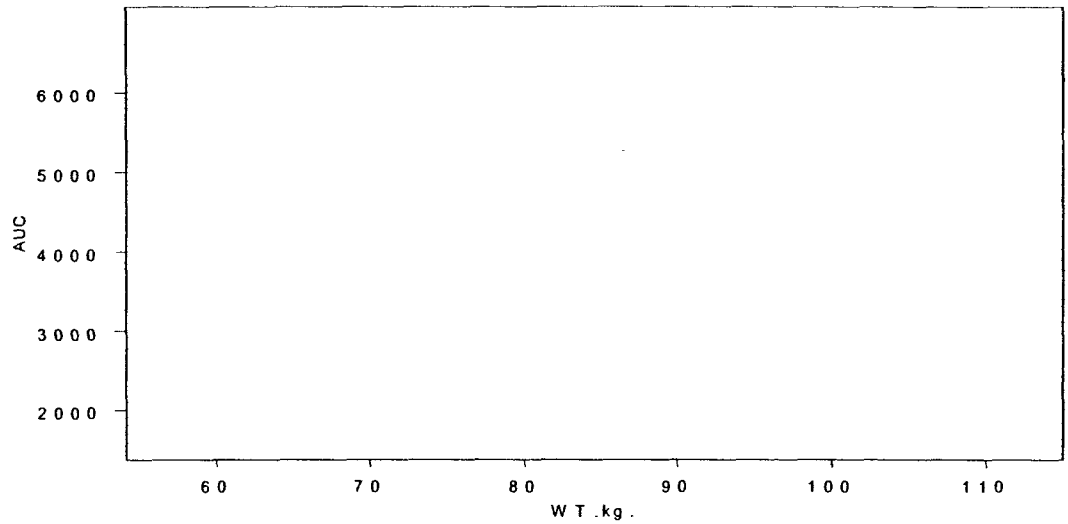
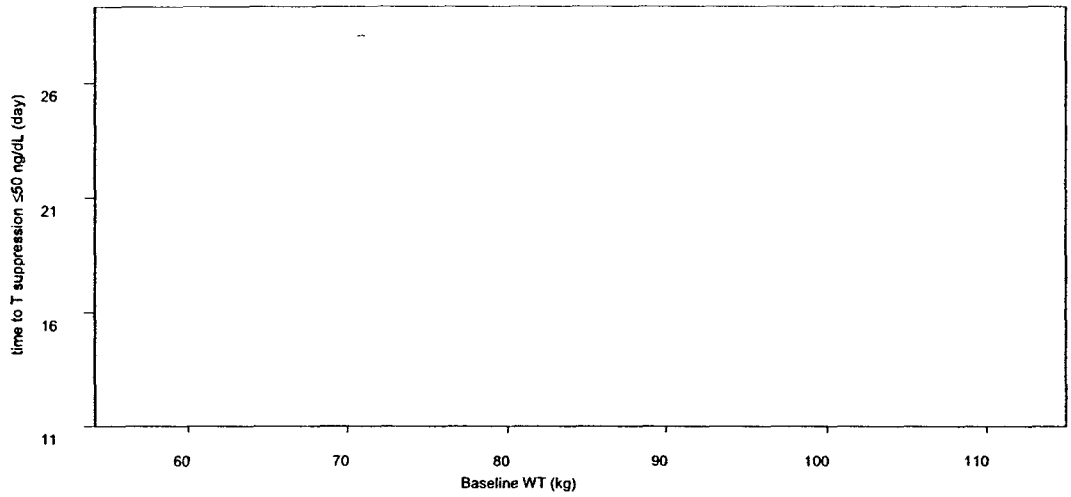


Figure 3. Relationship of Time to Testosterone Suppression (T ≤ 50 ng/dL) to Baseline Body Weight



A correlation analysis of time to T suppression by Baseline body weight demonstrated no relationship between these measures (P >0.05)

Renal Impairment: Slightly higher serum L levels would be expected in patients with pronounced renal dysfunction with no clinical relevance (Wechsel *et al* Eur Urol 1996;30:7-14). Although none of the patients in the clinical PK study had evidence of severe renal disease, 3 of 22

evaluable patients in the Study AGL9909 PK subset had urea nitrogen > 40 mg/dL and/or creatinine > 2 mg/dL at one or more time points during the study. Due to the wide therapeutic index of L, the PK variations observed were not of sufficient magnitude to affect the efficacy and safety of LA-2550 22.5 mg.

4.4 Extrinsic Factors

What extrinsic factors influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?

Drug-Drug Interactions

No PK drug-drug interaction studies were performed with LA-2550 22.5 mg. No drug-drug interactions have been described for other preparations of L acetate which does not appear to be metabolized by Cytochrome P450 or other phase I or phase II pathways that could lead to metabolic interactions. Because L is primarily metabolized via peptidase(s) (Chriap & Sorkin Drugs & Aging 1991;1:487-509), and is less than 50 % bound in the plasma (PDR 1999), PK drug-drug interactions are unlikely to be observed with LA-2550 22.5 mg. The effect of L on CYPs is unknown.

4.5 General Biopharmaceutics

What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparative exposure?

The formulations used in AGL-9909 are identical to the to-be-marked formulation and no formulation or significant manufacturing changes were implemented during the clinical trials. The two different lots (#1252 and #1272) of LA-2550 22.5 mg were used in the AGL 9909. Both formulations used in the phase 3 study (AGL 9909) were identical. The L acetate drug substance used for these lots was from two different manufacturers [redacted] and these lots delivered the same mass of L acetate and polymer. All patients included in the PK analysis received Lot 1252 for both injections. LA-2550 22.5 mg is designed to deliver 22.5 mg of L acetate over a three-month (84-day) from an injection volume of 0.375 mL of study drug.

What are the differences between clinical formulation and to be marketed formulation?

The formulation used in Study AGL 9909 is identical to the to-be-marked formulation.

4.6 Analytical

	LEUPROLIDE	TESTOSTERONE
Study No.	AGL9909	AGL9909
Type of Biological Fluid		
Assay Method	RIA	RIA
Sensitivity (LOQ)	ng/mL	ng/dL
Recovery	NA	
Linearity	ng/mL	ng
QC Sample	ng/mL	ng/dL
Inter-Assay Precision	%	%
Inter-Assay Accuracy	%	%
QC Sample	ng/mL	ng/dL
Intra-Assay Precision	%	
Intra-Assay Accuracy	%	NA
Selectivity (parent/metabolites)	%	%
Cross-Reactivity	%	%

*(<0.1 ng/mL)

LEUPROLIDE: Serum L concentrations were measured by a RIA method. To decrease the potential for metabolite cross-reactivity in the assay, serum samples were subjected to purification procedure, involving prior to the RIA determination. The validated range of the assay was ng/mL. Samples with concentrations above ng/mL were diluted and re-assayed.

TESTOSTERONE: T was first extracted from serum with hexane/ethyl acetate, and then further purified with using elution with ethanol in hexane. The purification had a recovery of approximately %. Assay precision was within % for intra-assay and inter-assay determinations at concentrations between ng/dL. The lower limit QC testosterone sample (ng/dL) had a bias of %. Intra-assay and inter-assay precision for the lower limit QC samples were between and %.

***In vitro* Dissolution (Method T549)**

The dissolution method used an aqueous medium composed of 90 % 25 mM aqueous 4-morpholinoethanesulfonic acid, 10 mM zinc acetate at pH 6.0 and 10% 2-propanol. The product sample was incubated at C with mixing at cycles per minute. Release medium samples were taken at specified times through 72 hours and analyzed by for cumulative percent release of LA-2550 22.5 mg. The T549 release profile had inflection points at 6, 18 to 24 and 48 to 54 hours. The 6- and 48-hour sampling times were selected as two of the three time points required for the extended release test method specifications. The 18-hour sampling time was selected as the second sampling time because its range of L release values did not overlap with the range at 6 or 48 hours.

In vitro dissolution performed using organic solvents has no physiological relevance.

Table 1. *In vitro* Dissolution Data from Different Batches by Method T549

Extended Release (hour)	5°C ± 2°C						
	Lot 1252	Lot 1272	Lot 1274	Lot 1381			
	18 Months	12 Months	9 Months	12 Months	0 Month	3 Months	6 Months
6							

18	
48	

Table 2. Sponsor's Proposed *in vitro* Dissolution Specifications

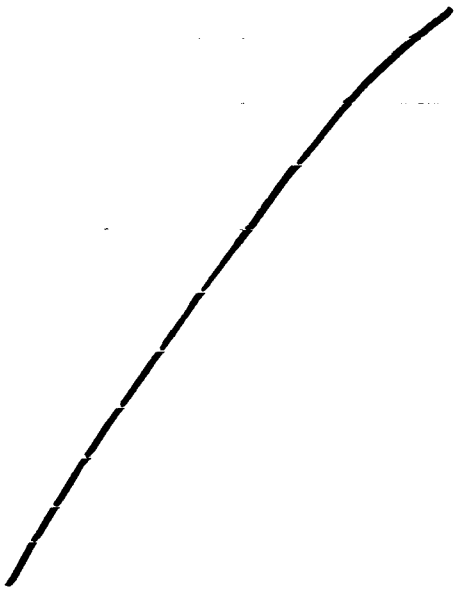


Table 3. OCPB's proposed *in vitro* Dissolution Specification

The following *in vitro* dissolution specifications for the acceptance criteria were accepted by the sponsor on 07/12/02 (facsimile received on 07/12/02). In addition, the sponsor proposed to revise the instructions to clarify that Tier 2 testing will be performed if any of the three conditions (mean, 5 of 6 units, individual units) fail to meet the dissolution acceptance criteria. These acceptance criteria were acceptable to the Division.

Extended Release Sampling Time	Mean % of Theory 22.5 mg	Not less than 5 of 6 units are within ± 10 % of mean specification values	No individual unit is more than ± 15 % of mean specification values
6 hr	NMT [redacted] %	NMT [redacted] %	NMT [redacted] %
18 hr	[redacted] %	[redacted] %	[redacted] %
48 hr	NLT [redacted] %	NLT [redacted] %	NLT [redacted] %

NLT = not less than; NMT = not more than

15 pages redacted from this section of the approval package consisted of draft labeling

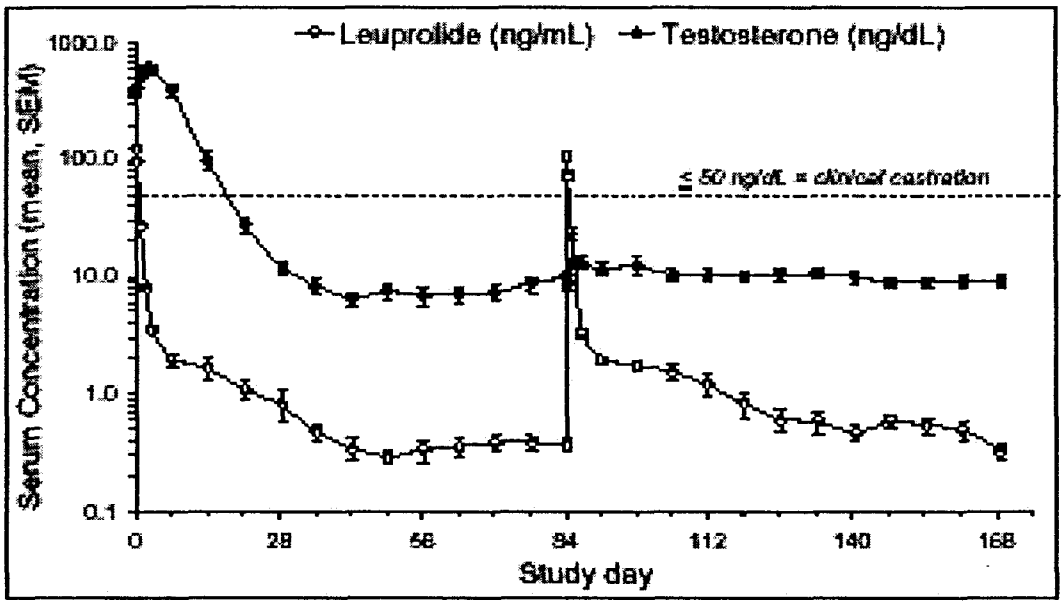
6.2 Individual Study Reviews

AGL 9909 Phase III Study

Of a subset of 25 adult male patients with advanced prostate cancer during treatment with LA-2550 22.5 mg every 3 (84 days) months for 6 months (168 days), the PK/PD of L were evaluated in 22 patients.

Three of the 25 patients enrolled in the PK subset were excluded from the PK analysis. One patient did not receive a full dose and did not complete the study. The other patient was excluded because the number of L measurements after Month 3 (Day 84) was insufficient to permit calculation of the required PK parameters. Lastly, serum L was not measured after Month 3 in one patient who experienced a breakthrough at Day 49 (T 112 ng/dL) after achieving castrate suppression at Day 21. 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 concentrations remained ≤ 50 ng/dL throughout the remainder of the study.

Figure 4. Pharmacodynamic Response to LA-2550 22.5 mg (AGL 9909)
Pharmacodynamic response to LA-2550 22.5 mg showing serum levels of L (open circles) and testosterone (closed circles) after two consecutive SC injections at 3 month intervals in patients with advanced prostate cancer (n = 22). Doses administered on Days 0 and Month 3 (84 days)

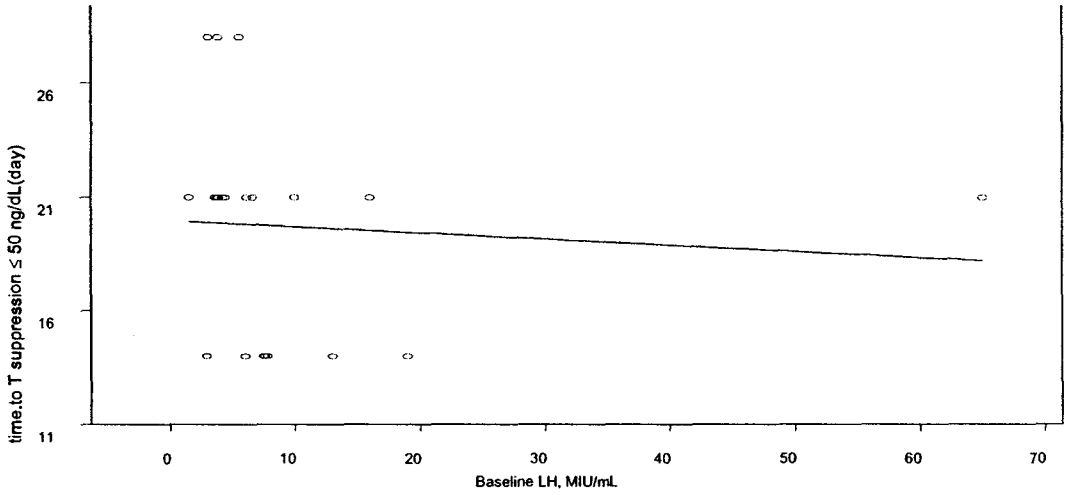


The PK profile of L in serum after each administration of LA-2550 22.5 mg was multi-phasic (Figure 4). Serum concentrations rose rapidly (> 100 ng/mL) after each dose, and then declined over the next several days. Mean Day 84 serum L concentrations were 0.34±0.21 ng/mL and 0.30±0.19 ng/mL for the two dosing intervals, respectively. Mean serum L during the plateau phases ranged from approximately 0.2 – 2 ng/mL. After the first dose, the mean total L serum AUC was 3,646±1,100 ng hr mL^{-1}, of which 1,419 ng hr mL^{-1} (39%) occurred during the plateau phase. After the second dose, the mean total L serum AUC was 3,880±921 ng hr mL^{-1}, of which 1925 ng hr mL^{-1} (50%) occurred during the plateau phase. The average serum concentrations of L during the plateau phases (based on the mean plateau phase AUCs) were 0.75 ng/mL (first

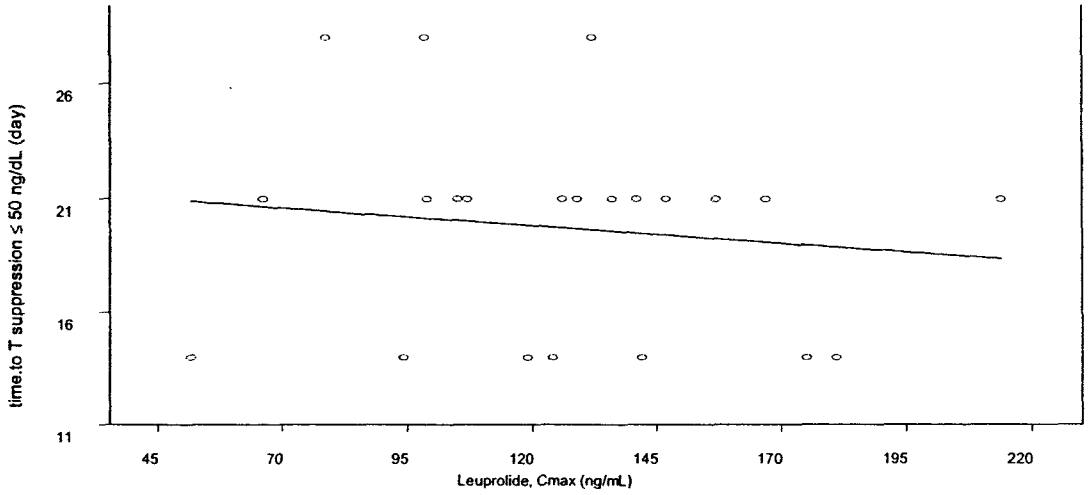
dose) and 0.96 ng/mL (second dose). From the reported clearance of IV L acetate (139 mL/min) (Sennello RT *et al* J Pharm Sci 1986;75:158-60), the average rate of L acetate delivery from the LA-2550 22.5 mg depot was between 150-190 µg/day during the plateau phases.

Serum L fell below the assay detection limit (— ng/mL) at one or more time points in 12 of 22 patients after the first dose, and in 3 of 22 patients after the second dose. However, serum L levels during the last two weeks of the first dosing interval were measurable (——— ng/mL) in 21 of 22 patients, and the mean (median) Month 3 (Day 84) levels were 0.34 ± 0.21 ng/mL (0.28 ng/mL). After the second dose, serum L concentrations during the last two weeks of the dosing interval were measurable (——— ng/mL) in 21 of 22 patients, and the mean (median) Month 3 (Day 84) concentrations were 0.30 ± 0.19 ng/mL (0.29 ng/mL).

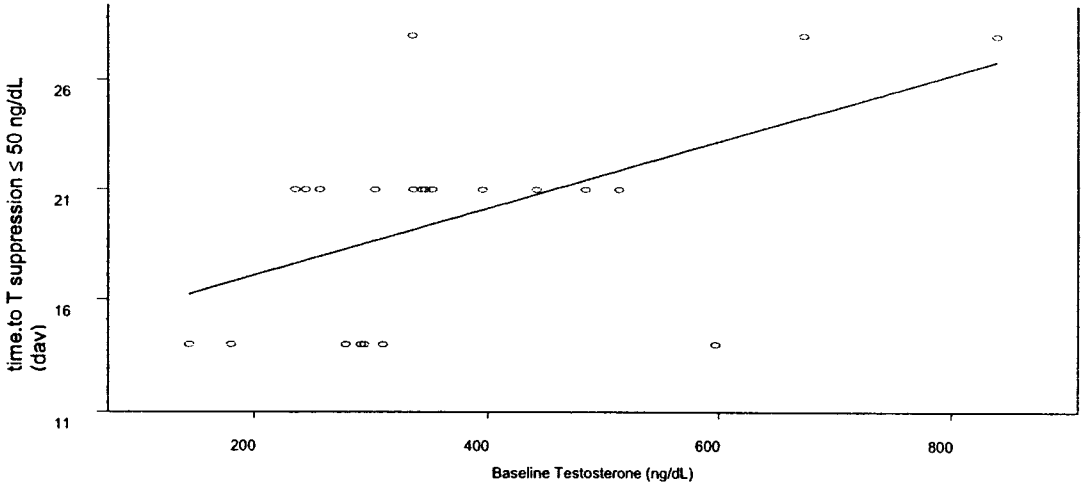
Figure 5. Analyses of Testosterone Suppression Response Related to Baseline LH, Baseline Testosterone, and Cmax Leuprolide (Subset of PK Patients, n=22)



- No effect of Baseline LH concentration on time to T suppression (P>0.05)



- No effect of Cmax L on time to T suppression (P>0.05)



- Analysis of the effect of Baseline T concentration on time to T suppression showed a statistically significant positive correlation (P=0.009). Patients with higher Baseline T achieved castrate T suppression more slowly than those patients with lower Baseline T. However, 100% of patients in the PK subset reached castrate testosterone suppression by Month 1 (Day 28)

In addition, analysis of the effect of Baseline T concentration on time to T suppression showed a highly statistically significant positive correlation in the clinical study (AGL9909; n=117) (P<0.001). However, 99 % of patients that received a full dose at Baseline reached castrate T suppression by Month 1.

Table 4. Summary of LA-2550 22.5 mg Pharmacokinetic Parameters After the First of Two Doses Given at 84-Day Intervals to Patients with Advanced Prostate Cancer (n=22)

	Burst Phase (Day 0-3)			Plateau Phase (Day 3-84)				Total (Day 0-84)	
Subj. No.	AUC ng hr ml^{-1}	Cmax ng/ml	Tmax hr	AUC ng hr ml^{-1}	Cmax ng/ml	Cmin ng/ml	Clast ng/ml	AUC ng hr ml^{-1}	F [a] %
0101									
0201									
0401									
0402									
0901									
1601									
1802									
1803									
1902									
2001									
2201									
2202									
2203									
2601									
3001									
3002									
3003									
3004									
3005									
3006									
3101									
3102									
Mean	2227	126.8	4.59	1419	2.4	0.15	0.344	3646	129
SD	516	38.8	1.6	770	1.6	0.08	0.21	1100	39
RSD	23	30.6	34.6	54.3	69	51	61.5	30.2	30
Median	2260	128	3.9	1110	1.9	BLOQ	0.28	3305	117
Min									
Max									

[a] Bioavailability (F) based on reported AUC of intravenous leuprolide.
[b] Concentration 84 days after dosing.
BLOQ, below assay limit of quantitation (ng/ml); NS, Not measured

Table 5. Summary of LA-2550 22.5 mg Pharmacokinetic Parameters After the Second of Two Doses Given at 84-Day Intervals to Patients with Advanced Prostate Cancer (n=22)

	Burst Phase (Day 0-3)[a]			Plateau Phase (Day 3-84)				Total (Day 0-84)	
Subj. No.	AUC ng hr ml^{-1}	Cmax ng/ml	Tmax hr	AUC ng hr ml^{-1}	Cmax ng/ml	Cmin ng/ml	Clast[b] ng/ml	AUC ng hr ml^{-1}	F[c] %
0101									
0201									
0401									
0402									
0901									
1601									
1802									
1803									
1902									
2001									
2201									
2202									
2203									
2601									
3001									
3002									
3003									
3004									
3005									
3006									
3101									
3102									
Mean	1955	107.1	4.5	1925	2.7	0.25	0.30	3880	136.9
SD	706	50.0	1.5	851	1.1	0.18	0.19	921	32.5
RSD	36.1	46.6	33.1	44.2	40	74	62	23.7	23.7
Median	1930	105	3.9	1685	2.5	0.18	0.28	3615	128
Min									
Max									

[a] Days after administration of second dose.
[b] Concentration three months (84 days) after dosing.
[c] Bioavailability (F) based on reported AUC of intravenous leuprolide.
BLOQ, below assay limit of quantitation (ng/ml); NS, Not measured.

AGL 9802 Phase I Study (Eligard 7.5 mg)
NDA 21-343
SYNOPSIS

Name of Active Ingredient:		
Leuprolide acetate		

Title of Study: A Two-Month, Open-Label, Noncontrolled, Fixed-Dose Study to Evaluate the Safety, Tolerance, and Pharmacokinetics of a Single Monthly Dose of LA-2500 (7.5 mg Leuprolide Acetate SC) in Orchiectomized Subjects with Advanced Prostatic Cancer

Studied period (years): 2 months
Date of first enrollment: 2/10/99
Date of last completed: 5/26/99

Phase of Development: Phase 1 Pharmacokinetic

Objectives: The objectives of this study were to evaluate the safety, tolerance, and pharmacokinetic (PK) profile of leuprolide acetate following a single monthly dose of LA-2500 in orchiectomized subjects with advanced prostate cancer.

Methodology: This was a noncontrolled, noncomparative study. All subjects received a single dose of the study drug and were followed for two months thereafter. Subjects received one subcutaneous injection of LA-2500 into the upper right or upper left quadrant of the abdomen using a half-inch, 20-gauge [redacted] hypodermic needle.

Number of subjects (planned and analyzed): 8 subjects were enrolled and analyzed.

Diagnosis and main criteria for inclusion: All subjects were male, between the ages of 45-85 years, had adenocarcinoma of the prostate, and had been orchiectomized at least two months prior to study start. Subjects were not receiving hormonal therapy and were not anticipated to need hormonal, anti-androgen, radio-, chemo-, immuno-, or surgical therapy for prostate cancer during the course of the study.

Test product, dose and mode of administration, batch number: The investigational product, LA-2500, was supplied in two, separate, sterile syringes and was mixed immediately prior to administration. One syringe contained the polymer formulation, ATRIGEL® Delivery System, consisting of [redacted]% w/w Poly(DL-lactide-co-glycolide) (PLGH) and [redacted]% w/w *N*-methyl-2-pyrrolidone) (NMP). The other syringe contained 11.4 mg of leuprolide acetate. Due to the viscous nature of the formulation, an overage of polymer solution and drug substance was provided to ensure delivery of 250 mg of the formulation and 7.5 mg of leuprolide acetate. Test article was manufactured by Atrix Laboratories. The lot number of the LA-2500 used in the study was 1105.

Duration of treatment: The approximate duration of treatment after the single depot LA-2500 injection, as indicated by measurable serum leuprolide levels, ranged from 28-49 days (mean=37 days).

Reference therapy, dose and mode of administration, batch number: N/A

CRITERIA FOR EVALUATION:

Pharmacokinetics: Blood samples for leuprolide PK analyses were taken at all scheduled visits beginning with the Baseline (pre-dose) visit.

Safety: Clinical laboratory measurements (hematology, coagulation, serum chemistry, urinalysis) were assessed for safety at Screening, Hours 24, 72, Days 7, 14, 28, and 56 for all subjects. Additionally, assessment of safety was measured via the collection of adverse event information at all visits beginning with the Baseline visit. Vital signs, including heart rate, blood pressure, respiratory rate, and temperature were collected for safety at Screening, Baseline, Minute 30, Hours 4, 12, 24, 48, and 72, and Days 28 and 56.

Statistical methods: Serum concentrations of leuprolide were summarized as mean, standard deviation, % relative standard deviation, N, median, minimum, and maximum based upon nominal times. Descriptive statistics were also determined separately for the two study centers. Plots of serum concentration versus time data were prepared using nominal times for mean concentration plots and actual times for individual concentration plots.

Pharmacokinetics parameters included the maximal observed leuprolide concentration (C_{max}), the time of maximal serum concentration (T_{max}), the time of last measured leuprolide concentration in serum (tldc), and area under the leuprolide serum concentration versus time curve (AUC) for various time periods (0-28

days, 0-tldc days, 28-tldc days and potentially other time intervals). The AUC was determined by linear trapezoidal interpolation for the time limits (0-tdlc) and (0-28 days), which is the anticipated dosing interval. A third AUC parameter, AUC(28-tldc) was determined as the difference between AUC(0-tldc) and AUC(0-28). Actual times were used for the pharmacokinetic analysis. Summary statistics for pharmacokinetic parameters were performed for all subjects combined and for subjects within the two treatment centers.

Clinical laboratory tests and analysis of adverse events were analyzed using descriptive statistics (mean ± standard deviation) where possible to assess the safety of study drug, laboratory measurements (hematology, coagulation, serum chemistry, urinalysis), adverse events, and concomitant medications.

SUMMARY - CONCLUSIONS

PHARMACOKINETIC RESULTS: Following subcutaneous administration of leuprolide acetate there was an initial rapid absorption phase with maximal concentrations observed at 2-6 hours. The serum leuprolide concentrations fell slowly over 4-6 days and remained detectable for at least 28 days in all subjects. It was common to observe a "bump" or increase in concentration within the first 10 days, followed by a plateau period where concentrations declined very slowly over several weeks. The mean maximal concentration was 26.3 ±12.6 ng/ml with a mean Tmax of 3.79 ±1.39 hours. Serum leuprolide levels were detectable for a mean of 37 days (range 28-49 days). The AUC(0-tldc) was 999 ±247 ng*h/ml and was characterized by low inter-subject variability (CV=— %). Only about 10% of the total AUC was observed after 28 days, indicating that accumulation following multiple dosing at 28-day intervals would be small. Pharmacokinetic parameters were similar comparing subjects by study site; however, a statistical comparison was not performed due to the small sample size.

SAFETY RESULTS: No serious treatment-related adverse events were reported during the study. There were no discontinuations owing to adverse events. No trends for clinically relevant abnormalities of laboratory safety tests were noted during the study.

The all-causalities adverse events reported by the most subjects were: discomfort upon injection (7/8), bruise at injection site (3/8), hot flashes (2/8), and gastrointestinal disturbances (2/8).

The total treatment-related, treatment-emergent adverse events reported by the subjects were: mild discomfort upon injection (3/8), mild hot flashes (1/8), and mild erythema at the injection site (1/8).

Discomfort upon injection of LA-2500 was mild and transient, lasting only a few seconds in six subjects, and for less than a few minutes in one subject. One subject reported no discomfort upon injection.

There was no evidence of local hypersensitivity reactions at the site of injection in any subjects. There was no evidence of any acute or chronic systemic hypersensitivity responses in any subject.

CONCLUSION: LA-2500 administered as a single, monthly, subcutaneous dose in orchiectomized subjects with adenocarcinoma of the prostate was associated with a favorable safety and toleration profile.

The course of serum leuprolide concentration over time was consistent between subjects. Leuprolide was detectable in all subjects at Day 28. The overall pharmacokinetic profile of LA-2500 administered subcutaneously indicates that a monthly dosing regimen should be appropriate to provide adequate, measurable serum leuprolide levels throughout the dosing interval time period.

AGL 9904 Phase III Study (Eligard 7.5 mg)
NDA 21-343

Name of Company:	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
Atrix Laboratories, Inc.	Volume:	
Name of Finished Product: LEUPROGEL™ 7.5 mg		
Name of Active Ingredient: Leuprolide acetate	Page:	

Title of Study: A Six-Month, Two-Part, Sequential, Open-Label, Fixed-Dose Study to Evaluate the Safety, Tolerance, Pharmacokinetics and Endocrine Efficacy of Monthly Doses of LEUPROGEL™ 7.5 mg in Patients with Advanced Prostate Cancer

Studied period (years): 14 months **Phase of Development:** Phase 3

Date of first enrollment: September 27, 1999

Date of last completed: November 15, 2000

Objectives: The objectives of the study were: 1) To evaluate the safety and tolerance of monthly doses of LEUPROGEL™ 7.5 mg in patients with advanced prostate cancer. 2) To evaluate serum testosterone and LH levels following monthly doses of LEUPROGEL™ 7.5 mg in patients with advanced prostate cancer. 3) To determine the pharmacokinetic (PK) profile of serum leuprolide acetate following three monthly subcutaneous injections with LEUPROGEL™ 7.5 mg in a subset of patients with advanced prostate cancer.

Methodology: All patients were scheduled to receive six doses of LEUPROGEL™ 7.5 mg (Baseline and Months 1 through 5; 28-day months) subcutaneously injected into the upper right or upper left quadrant of the abdomen using a half-inch, 20-gauge hypodermic needle. Injections were administered immediately following drug preparation by a person trained to give SC injections. Each patient received the same fixed-dose study drug formulation. The formulation was identical to the to-be-marketed formulation.

LEUPROGEL™ 7.5 mg is designed to deliver 7.5 mg of leuprolide acetate from 250 milligrams of constituted study drug over a one-month (28-day) therapeutic period. The injection volume was 0.25 mL.

The primary efficacy variable in this open-label, fixed-dose study was serum testosterone concentration at the various sampling timepoints. Descriptive statistics (e.g., mean, standard error, minimum, maximum) were used to summarize the concentrations at each timepoint as well as to determine the mean and median time to testosterone suppression. Descriptive statistics were also used to evaluate testosterone data for acute-on-chronic and breakthrough responses following initial suppression.

Number of patients (planned and analyzed): 120 patients were enrolled and analyzed in the intent-to-treat dataset. In the analysis of testosterone suppression the intent-to-treat analysis involved carrying forward data to the end of the study for three patients who were withdrawn prior to completing the study. Testosterone suppression was also evaluated in an analysis of observed cases. In this dataset the data for the three withdrawn patients was not carried forward past the time they were withdrawn.

Diagnosis and main criteria for inclusion: All patients were male between the ages of 50-85 years and had adenocarcinoma of the prostate. Patients were not receiving hormonal therapy and were not anticipated to need hormonal, anti-androgen, radio-, chemo-, immuno-, or surgical therapy for prostate cancer during the course of the study.

Test product, dose and mode of administration, batch number: The investigational product, LEUPROGEL™ 7.5 mg, was supplied in two, separate, sterile syringes and was mixed immediately prior to administration. One syringe contained the polymer formulation, ATRIGEL® Delivery System, consisting of —% w/w Poly(DL-lactide-co-glycolide) (PLGH) and— % w/w *N*-methyl-2-pyrrolidone (NMP). The other syringe contained 11.4 mg lyophilized leuprolide acetate. The syringes were joined via the ——) connections on the syringes, and the formulation was passed between syringes until a homogenous mixture was obtained. Study drug was manufactured by Atrix Laboratories. The lot numbers of LEUPROGEL™ 7.5 mg used in the study were 1144 and 1199. The injection volume was 0.25 mL.

Duration of Treatment: LEUPROGEL™ 7.5 mg is designed to deliver 7.5 mg of leuprolide acetate over one month (28) days following injection. Of the 120 patients enrolled into the study, 117 received six once-monthly injections of study drug. One patient received three injections, one patient two injections, and one patient a single injection of study drug.

Reference therapy, dose and mode of administration, batch number: N/A

CRITERIA FOR EVALUATION:

Efficacy: The primary efficacy variable for this study was serum testosterone concentration. These concentrations were sampled at Baseline (Day 0) before injection of study drug. Post-injection testosterone concentrations were determined at Day 0: Hours 4 and 8, Days 1, 2, 3, 4, 7, 10, 14, 21, 28, Day 28: Hour 8,

Days 29, 31, 35, 42, 49, 56, 57, 59, 63, 70, 77, 84, 98, Month 4, Week 18, Month 5, Week 22, and Month 6. Data for Week 18 and Week 22 timepoints are only available for those patients not effected by Amendment No. 1.

Secondary measures of efficacy included serum LH concentrations (taken at the same times as for testosterone), measures of bone pain, urinary pain and symptoms, and WHO performance status scores.

Additionally, blood samples for pharmacokinetic analysis (serum leuprolide acetate quantitation) were taken at Baseline (Day 0), Hours 4 and 8, Days 1, 2, 3, 4, 7, 10, 14, 21, 28, Day 28: Hour 8, Days 29, 31, 35, 42, 49, 56, 57, 59, 63, 70, 77, and 84 for a subgroup of 20 patients only (Group A). Blood samples for evaluation of the efficacy variables T and LH were drawn at each visit.

Safety: Clinical laboratory measurements, including hematology, coagulation, and serum chemistry, were assessed for safety at all visits through Day 14, and then at Days 28, 42, 56, 70, 84, Month 4, Week 18, and Month 6 for all patients.

Assessment of safety was measured via the collection of adverse event information at all visits beginning with the Baseline visit.

Vital signs including heart rate, blood pressure, respiratory rate and temperature were documented at Screening, Baseline, and Days 7, 14, 28, 56, 84, and Months 4, 5, and 6.

Statistical methods: The primary efficacy variable in this study was serum testosterone concentration at the various sampling timepoints. Descriptive statistics (i.e., mean, standard error, minimum, maximum) were used to summarize the concentrations at each timepoint as well as to determine the mean and median time to testosterone suppression.

Secondary efficacy parameters included evaluation of serum LH concentrations, WHO performance status, bone pain, urinary pain, and urinary symptoms at the various sampling timepoints. These measures were summarized using descriptive statistics.

Clinical laboratory tests and analysis of adverse events were analyzed using descriptive statistics (mean ± standard error) where possible, to assess the safety of study drug via laboratory measurements (hematology, coagulation, serum chemistry, urinalysis), adverse events, and concomitant medications. Pharmacokinetic parameters were analyzed using descriptive statistics on the maximum leuprolide serum concentration (C_{max}), time of maximum serum concentration (T_{max}), and area under the leuprolide serum concentration versus time curve for various time periods. Observed values were to be used for C_{max} and T_{max}.

SUMMARY-CONCLUSIONS

EFFICACY RESULTS: Following six once-monthly doses of LEUPROGEL™ 7.5 mg, 100% of patients (observed patients dataset) who continued in the study through at least Day 14 reached castrate suppression of testosterone concentration, defined as testosterone concentration of ≤50 ng/dL for two consecutive timepoints approximately one week apart. By Study Day 28, 112 of the 119 (94%) patients remaining in the study had achieved testosterone suppression, and by Study Day 42, all 118 patients remaining in the study had achieved this measure. In addition, all of those patients who achieved castrate testosterone suppression (≤50 ng/dL) remained suppressed throughout the duration of the study. That is, no castrate suppression breakthroughs (defined as a testosterone concentration of >50 ng/dL after achieving suppression) were observed during the study. The median time to castrate suppression was 21 days, and the mean time to castrate suppression was 21.6 days. Additionally, patient PSA scores were reduced by an average of greater than 90% from Baseline during the study.

Very little change was observed throughout the study in terms of WHO performance status. At Baseline, 88% of patients were classified as fully active and this proportion remained at 88% through the end of the study suggesting no decrease in performance status during the study.

Bone pain, urinary symptoms, and urinary pain were assessed by patients during the study. All measures were low at Baseline and remained low during the study indicating good symptom control was maintained during the six months of the study.

Clinically, it is well recognized that brief symptomatic flare may occur following therapy with leuprolide acetate or other GnRH agonists, sometimes necessitating concomitant medication or other treatment. However, in this study, there was no increase in these symptom scores in the three days post-study drug dosing, suggesting that there were no flare symptoms. Over the course of the study there was a modest reduction in symptom scores from Baseline values. These overall results indicate that good symptom control was maintained during the six months of the study with no acute-on-chronic response following study injections.

Repeated monthly treatment of advanced prostate cancer patients with LEUPROGEL™ 7.5 mg, produced serum leuprolide profiles similar to those of other effective leuprolide depot formulations. After

an initial burst phase characterized by high (— ng/mL) serum concentrations, the formulation maintained relatively constant mean serum leuprolide levels (0.2–2 ng/mL) over the majority of each dosing interval. The bioavailability of LEUPROGEL™ 7.5 mg was greater than 90% and the rate of delivery of active drug was relatively constant during the plateau phase. There was no evidence of accumulation after repeated administration, with similar serum profiles observed after each dose.

The pattern of leuprolide exposure following monthly LEUPROGEL™ 7.5 mg administration was associated with suppression of testosterone to castrate levels in 100% of patients (observed-cases population). Thus, monthly LEUPROGEL™ 7.5 mg maintains constant suppression of testosterone secretion by maintaining serum leuprolide exposure at levels above the minimum required for complete inhibition of gonadotropic hormone release.

All study patients maintained testosterone suppression ≤50 ng/dL throughout the study with 97% of patients showing suppression below the more stringent ≤20 ng/dL level by Day 42 of the study. At Month 6 mean testosterone values were 6.1 ng/dL compared to 361.3 ng/dL at Baseline.

SAFETY RESULTS: The observed safety profile of LEUPROGEL™ 7.5 mg was similar to that of other products containing leuprolide acetate.

Common adverse events found in the treatment-related categories for this multi-dose study were: hot flashes, dizziness/giddiness, malaise/fatigue, testicular discomfort/atrophy, and injection site adverse events.

Injection site adverse events were typical of those associated with similar SC injectable products. No patients discontinued the study due to those events. There was no indication that a patient who reported an injection site adverse event would report recurrent events with subsequent injections. There were no trends to increased severity, frequency, or duration with subsequent injections. Injection site adverse events were very brief in duration, mild in severity, and sporadic in nature. No event provoked clinical concern.

Overall, LEUPROGEL™ 7.5 mg was found to have a favorable safety profile both systemically and locally and was well tolerated for up to six, monthly injections when administered to men with advanced prostate cancer.

OVERALL CONCLUSION: Following six once-monthly doses of LEUPROGEL™ 7.5 mg, 100% of patients who continued in the study through at least Day 14 reached castrate suppression of testosterone concentration, defined as testosterone concentration of ≤50 ng/dL for two consecutive timepoints approximately one week apart. By Study Day 28, 112 of the 119 (94%) patients remaining in the study had achieved testosterone suppression, and by Study Day 42, all 118 patients remaining in the study had achieved this measure. In addition, all of those patients who achieved castrate testosterone suppression remained suppressed throughout the duration of the study. Additionally, patient PSA scores were reduced by an average of greater than 90% from Baseline during the study.

Summaries of WHO performance status, bone pain, urinary symptoms, and urinary pain all indicated good symptom control was maintained during the six months of the study with no evidence of flare responses.

Repeated monthly treatment of advanced prostate cancer patients with LEUPROGEL™ 7.5 mg, produced serum leuprolide profiles similar to those of other effective leuprolide depot formulations. After an initial burst phase characterized by high (— ng/mL) serum concentrations, the formulation maintained relatively constant mean serum leuprolide levels (0.2–2 ng/mL) over the majority of each dosing interval. The bioavailability of LEUPROGEL™ 7.5 mg was greater than 90% and the rate of delivery of active drug was relatively constant during the plateau phase. There was no evidence of accumulation after repeated administration, with similar serum profiles observed after each dose.

Injection site adverse events were typical of those associated with other injectable SC products. There were no trends to increased severity and duration with subsequent injections. Injection site adverse events did not cause clinical concern. The majority of other adverse events noted—e.g. hot flashes, testicular atrophy, etc.—were those typically associated with testosterone suppression and consequent medical castration. No patients discontinued due to treatment-related adverse events.

Overall, LEUPROGEL™ 7.5 mg was found to have a favorable safety profile both systemically and locally and was well tolerated for up to six, monthly injections when administered to males with advanced prostate cancer.

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**21-379**	**Brand Name**	**Eligard 22.5 mg**
OCPB Division (I, II, III)	**DPE II**	**Generic Name**	**Leuprolide acetate**
Medical Division	**DRUDP**	**Drug Class**	**LHRL agonist**
OCPB Reviewer	**Myong-Jin Kim**	**Indication(s)**	**Palliative Treatment of Advanced Prostate Cancer**
OCPB Team Leader	**Ameeta Parekh**	**Dosage Form**	**Parenteral**
		Dosing Regimen	**22.5 mg**
Date of Submission	**9/26/01**	**Route of Administration**	**SC**
Estimated Due Date of OCPB Review	**6/21/02**	**Sponsor**	**Atrix Laboratories, Inc.**
PDUFA Due Date	**7/26/02**	**Priority Classification**	**3S**
Division Due Date	**7/03/02**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:	X	1	1	
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	X	2	2	
Population Analyses -				

Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:	X	1	1	
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X		6	
Total Number of Studies		3	3	

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date	**Myong-Jin Kim**	

CC: NDA 21-379, HFD-850 (L. Lesko, S. Huang), HFD-580 (A. Batra, M. Hirsch), HFD-870 (A. Parekh, H. Malinowski, J. Hunt), CDR (B. Murphy)
CP&B Briefing attendees on 06/27/02: A. Batra, S. Haidar, J. Hunt, A. Khan, H. Malinowski, and A. Parekh,

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/s/

Myong-Jin Kim
7/19/02 09:18:45 AM
PHARMACOLOGIST

Ameeta Parekh
7/22/02 03:44:44 PM
BIOPHARMACEUTICS
I concur

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-379	Brand Name	LA-2550
OCPB Division (I, II, III)	DPE II	Generic Name	Leuprolide acetate
Medical Division	DRUDP	Drug Class	LHRL agonist
OCPB Reviewer	Myong-Jin Kim	Indication(s)	Palliative Treatment of Advanced Prostate Cancer
OCPB Team Leader	Ameeta Parekh	Dosage Form	Parenteral
		Dosing Regimen	22.5 mg
Date of Submission	9/26/01	Route of Administration	SC
Estimated Due Date of OCPB Review	6/01/02	Sponsor	Atrix Laboratories, Inc.
PDUFA Due Date	7/26/02	Priority Classification	
Division Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:	X	1		
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	X	2		

Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:	X	1		
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X			
Total Number of Studies		3		

Filability and QBR comments		
	"X" if yes	**Comments**
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)		
Other comments or information not included above		
Primary reviewer Signature and Date	**Myong-Jin Kim**	
Secondary reviewer Signature and Date	**Ameeta Parekh**	

Filing Memo

Clinical Pharmacology and Biopharmaceutics Review

NDA: 21-379
Compound: 22.5 mg leuprolide acetate, extended-release formulation for 3 month LA-2550
Sponsor: Atrix Laboratories, Inc.

Date: 11/14/2001
Reviewer: Myong-Jin Kim

Background:

NDA 21-379 (Leuprogel™, IND [redacted]), an extended-release of 22.5 mg leuprolide acetate as a three-month subcutaneous injection for the palliative treatment of advanced prostate cancer, was submitted on 09/26/2001.

The pivotal phase 3 study of LA-2550 22.5 mg (AGL9909) was conducted to evaluate the pharmacokinetics and pharmacodynamics of leuprolide in a subset of 22 patients with advanced prostate cancer with LA-2550 22.5 mg every 3 months for 6 months.

The formulation used in Study AGL9909 represents the same drug formulation used in the to-be-marked product.

In addition to submitting AGL9909, the sponsor provided human pharmacokinetic and pharmacodynamic data from clinical studies (NDA-21-343) which are still under review.

Sponsor provided the following:
1. Human Pharmacokinetics and Bioavailability section summary, full study report, and labeling
2. Drug formulation, *in vitro* release testing, and delivered mass data
3. Bioanalytical assay and validation information for leuprolide and testosterone
4. Reference articles

Recommendation:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II find that the Human Pharmacokinetics and Bioavailability section for NDA 21-379 is fileable.

/S/

Myong-Jin Kim, Pharm.D. Date

/S/

Ameeta Parekh, Ph.D., Team Leader Date

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/s/

Myong-Jin Kim
11/14/01 04:05:14 PM
PHARMACOLOGIST

Ameeta Parekh
12/5/01 11:15:42 AM
BIOPHARMACEUTICS
I concur

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

Abuse Liability Review

This NDA application is not the subject of an abuse liability review. CLR 7/9/02