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APPLICATION NUMBER:

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NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	NDA 213150
Regulatory Pathway:	505(b)(2)
Supporting document/s:	0001
Applicant's letter date:	July 2nd 2019
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Product:	Leuprolide Acetate (FENSOLVI)
Indication:	Central Precocious Puberty (CPP)
Applicant:	Tolmar International LTD
Review Division:	DMEP
Reviewer:	Jeffrey Quinn, PhD
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Review completion date:	March 17th, 2020

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1 Executive Summary

Introduction

Tolmar submitted a new drug application (NDA 213150) for FENSOLVI (45 mg, leuprolide acetate), a synthetic nonapeptide analog of naturally occurring gonadotropin releasing hormone (GnRH) agonist, for the treatment of central precocious puberty (CPP) in pediatric patients 2 years of age and older. FENSOLVI (45 mg, leuprolide acetate) will be administered subcutaneously, one injection every 6 months.

Tolmar did not submit new nonclinical studies to support NDA 213150. The Sponsor cites Eligard (NDA 21731; Tolmar International, Inc, or TIL) and Lupron Depot-PED (NDA 20263; AbbVie Endocrine, Inc) for the nonclinical information needed to support approval of Fensolvi.

1.1 Recommendations

1.1.1 Approvability

Nonclinical data supports approval of NDA 213150

1.1.2 Additional Nonclinical Recommendations

No additional nonclinical studies are recommended.

1.1.3 Labeling Recommendations

Section 13 of the FENSOLVI (leuprolide acetate) drug label should include information on impairment of fertility. The Sponsor indicated that impairment of fertility language would be included in the PLLR update of the ELIGARD label/PI and this information would be reiterated in the FENSOLVI label.

Prior to conversion of the Eligard drug label to PLR in 2010, section 8.1 described major fetal abnormalities as occurring in rabbits, not rats, as described in the current label. An internal analysis of the related labeling source materials indicates that major fetal abnormalities were observed in rabbits but not in rats. The ELIGARD and FENSOLVI labels will be updated to reflect these changes.

1.2 Brief Discussion of Nonclinical Findings

The referenced NDAs for Eligard and Lupron Depot-PED, and the literature, provide the nonclinical profile of leuprolide acetate necessary to support approval of Fensolvi.

- FENSOLVI (leuprolide acetate) is a GnRH agonist that inhibits the release of FSH and LH through pituitary desensitization and down-regulation of the GnRH receptors. Down-regulation leads to suppression of gonadotropin release and has indicated the use of GnRH agonists for therapeutic treatment of central precocious puberty (CPP).

- An acceptable quality assessment of the leuprolide acetate active moiety relative to referenced NDAs and DMFs (see section 2.2) provides an adequate basis to extrapolate the necessary nonclinical information to Fensolvi, and specifically the reproductive toxicology and carcinogenicity information used to inform sections 8 and 13 of the drug label.

- Regarding the excipients in the FENSOLVI drug product, studies conducted with ATRIGEL and NMP indicate that at the proposed levels of exposure these excipients represent a limited risk to children with central precocious puberty (CPP).

2 Drug Information

2.1 Drug: FENSOLVI (leuprolide acetate)

Chemical Name

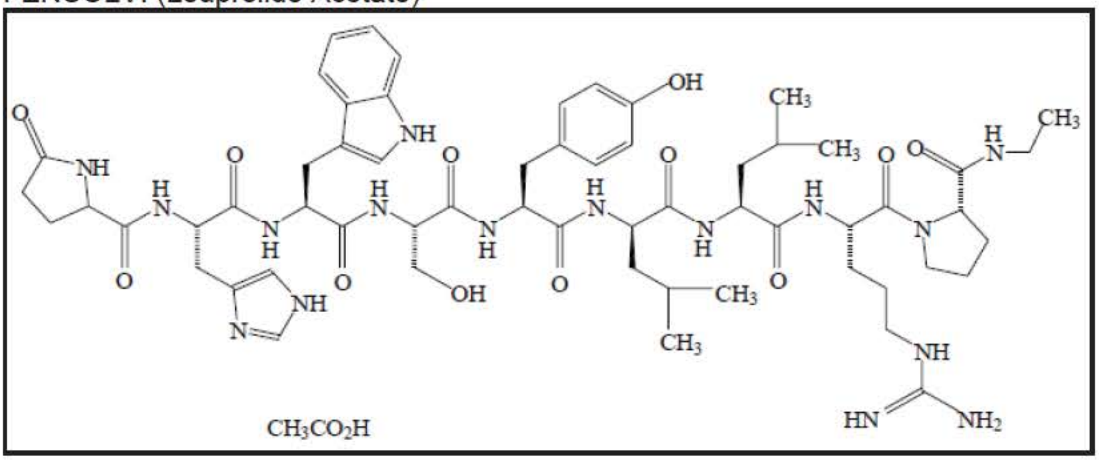
5-Oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tryosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide monoacetate (salt)

Molecular Formula/Molecular Weight

$C_{59}H_{84}N_{16}O_{12}$ (net)
$C_{59}H_{84}N_{16}O_{12} \cdot C_2H_4O_2$ (leuprolide acetate) 1208.6 (monoisotopic mass)

Structure or Biochemical Description

FENSOLVI (Leuprolide Acetate)



Pharmacologic Class

Gonadotropin releasing hormone (GnRH) agonist or Luteinizing Hormone Releasing Hormone (LHRH) agonist

Planned Clinical Route of Administration

Subcutaneous Injection

2.2 Relevant INDs, NDAs, BLAs and DMFs

INDs: (b) (4) (b) (4); (b) (4) 64,779
NDAs: 20263; 21343; 21379; 21488; 21731
DMFs: (b) (4); (b) (4) (b) (4) (for leuprolide acetate); (b) (4) for poly (D, L-lactide) and its copolymers; (b) (4) & (b) (4) for *N*-Methyl-2-Pyrrolidone (NMP)

2.3 Drug Formulation

The drug product, FENSOLVI (45 mg, leuprolide acetate for injectable suspension) is a polymeric matrix formulation of leuprolide acetate intended for subcutaneous injection once every 6 months. The FENSOLVI 45 mg drug product consists of a two-syringe mixing system and a sterile needle. One syringe, Syringe A, contains 434 mg of the ATRIGEL delivery system,

a sterile, polymeric solution of (b) (4) poly (DL-lactide-co-glycolide) (PLG) and (b) (4) N-methyl-2-pyrrolidone (NMP). The other syringe, Syringe B, contains (b) (4) mg leuprolide acetate. (b) (4) 45 mg of leuprolide acetate.

PLG is a biocompatible, bio-absorbable polymer that is a member of a family of poly(α-hydroxy acids) that are bio-absorbable polymers used widely in medical devices, such as absorbable sutures. NMP is a biocompatible solvent (b) (4)

FENSOLVI (leuprolide acetate) Target Composition

Composition of Syringe A: ATRIGEL® Delivery System		
Component	**Function**	**Finished Product (mg/unit)**
85:15 Poly(DL-lactide-co-glycolide) (PLG)	(b) (4)	(b) (4)
N-methyl-2-pyrrolidone (NMP)	(b) (4)	
Composition of Syringe B: Lyophilized Leuprolide Acetate		
Component	**Function**	**Finished Product (mg/unit)**
Leuprolide Acetate	Active drug substance	(b) (4)
Composition of ELIGARD® 45 mg Constituted Drug Product (dose delivered)		
Component	**Function**	**Finished Product (mg/unit)**
Leuprolide Acetate	Active drug substance	45 [b]
85:15 Poly(DL-lactide-co-glycolide) (PLG)	(b) (4)	165
N-methyl-2-pyrrolidone (NMP)	(b) (4)	165

[a] (b) (4)

[b] 45 mg leuprolide acetate is equivalent to approximately 41.7 mg leuprolide free base.

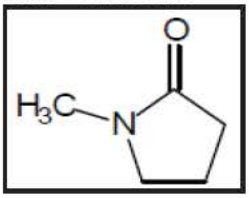
2.4 Comments on Novel Excipients

N-Methyl-2-Pyrrolidone (NMP)

Synonyms/codes: Pharmasolve, 1-methyl-2-pyrrolidone, N-methylpyrrolidone, N-methylpyrrol and H-20417

CAS registry No.: 872-50-4
Molecular weight: 99.13

NMP Structure



N-Methyl-2-Pyrrolidone (NMP) is an inert, stable, solvent used as a solubilizing agent and penetration enhancer for topical pharmaceutical products. Tolmar conducted a number of studies to demonstrate the safety of NMP used in the various ELIGARD formulations.

The literature reports numerous studies in bacteria, human cell lines, mice, rats, dogs and humans. NMP is classified as a teratogenic compound in PubChem and studies in mice, rats, dogs and human subjects have yielded conflicting results.

(b) (4)

The PDE was based on a study in Wistar rats that were exposed by inhalation to 150 ppm NMP for 6 hours/day, daily from days 7-20 of gestation and were then allowed to litter. No maternal toxicity was detected, and litter size was unaffected by treatment. No physical abnormalities were described. The offspring were reduced in weight, the difference being statistically significant up to week 5 after birth (equivalent to age 2 to 12 years in humans). Pre-weaning development was impaired as was higher cognitive function related to solving of difficult tasks. Basal function of the CNS was normal and there were no effects on learning of low-grade tasks. A NOEL was not established.

N-Methyl-2-pyrrolidone was not found to be genotoxic in various *in vitro* and *in vivo* studies and carcinogenic effects were not observed in long-term studies of NMP in rats after either inhalation (Lee, 1987) or oral exposure (Malley, 2001). However, the incidences of pre-neoplastic lesions and adenomas and carcinomas of the liver were increased in mice of both genders in the high dose group of a feeding study (Malley, 2001).

NMP is quickly distributed to most organs, with a relatively high concentration in the sexual organs and repeat exposure has been linked to infertility in male rats. The half-life of unchanged NMP in the plasma after oral or dermal administration exposure is 9 to 12 hrs in rats. The LD_{50} for NMP administered subcutaneously exceeds 2000 mg/kg in rats. Based on the HED, the theoretical NMP LD_{50} in adult human subjects would exceed 19 g. The theoretical NMP LD_{50} in 2-year-old children (youngest age proposed in current study) would exceed 3.9 g in females (12 kg) and 4 g in males (12.5 kg) and represent doses of NMP that are 24-fold higher than the concentration of this excipient delivered in the FENSOLVI 45 mg dose.

Administration of FENSOLVI 45 mg delivers a 165 mg dose of NMP. This value exceeds the permissible daily exposure (PDE) of NMP (5.3 mg/day) by 31-fold. Considering the short half-life, lack of acute toxicity at clinically relevant doses and the extended time between dosings the 165 mg dose of NMP (once every 6 months) does not represent a significant safety risk to children with CPP.

Polylactic/Polyglcolic Acid Polymers and Copolymers (ATRIGEL - PLGH)

50/50 Poly (DL-lactide-co-glycolide) COOH (PLGH) belongs to the family of poly (α-hydroxy acids) including polylactide and polyglycolide which are commonly used in sutures, medical devices, and drug delivery systems. The polymers and copolymers degrade in the aqueous environment of human tissues to lactic acid and glycolic acids, which are eliminated from the body via Krebs cycle metabolism as carbon dioxide and water. Tolmar conducted a number of studies that demonstrated the safety and tissue response to the 50:50 poly (DL-lactide-co-glycolide) COOH used in FENSOLVI (leuprolide acetate).

2.5 Comments on Impurities/Degradants of Concern

FENSOLVI is identical to the approved drug product ELIGARD 45 mg for the palliative treatment of advanced prostate cancer. The levels of impurities/degradants represented in the final drug product should not pose any unique risks to children with central precocious puberty.

2.6 Proposed Clinical Population and Dosing Regimen

Pediatric patients 2 years of age and older with central precocious puberty (CPP). FENSOLVI will be administered subcutaneously, one injection (45 mg) every 6 months.

3 Studies Submitted

Tolmar did not submit any new nonclinical studies with this application and intends to use the approved product ELIGARD 45 mg and Lupron Depot PED as reference drug products.

The nonclinical information in sections 8 and 13 of both drug labels describe the same data/studies conducted to address reproductive toxicology, infertility, and carcinogenicity.

4 Pharmacology

4.1 Primary Pharmacology

Drug Activity Related to Proposed Indication

FENSOLVI (leuprolide acetate) is a synthetic oligopeptide (9 amino acids) analog of the naturally occurring gonadotropin releasing hormone (GnRH) that, when administered continuously, inhibits pituitary gonadotropin secretion and suppresses testicular and ovarian steroidogenesis. GnRH agonists, like leuprolide acetate, inhibit the release of FSH and LH through pituitary desensitization and down-regulation of the GnRH receptors. Down-regulation leads to suppression of gonadotropin release and has indicated the use of GnRH agonists for therapeutic treatment of central precocious puberty (CPP) for over three-decades.

4.3 Safety Pharmacology

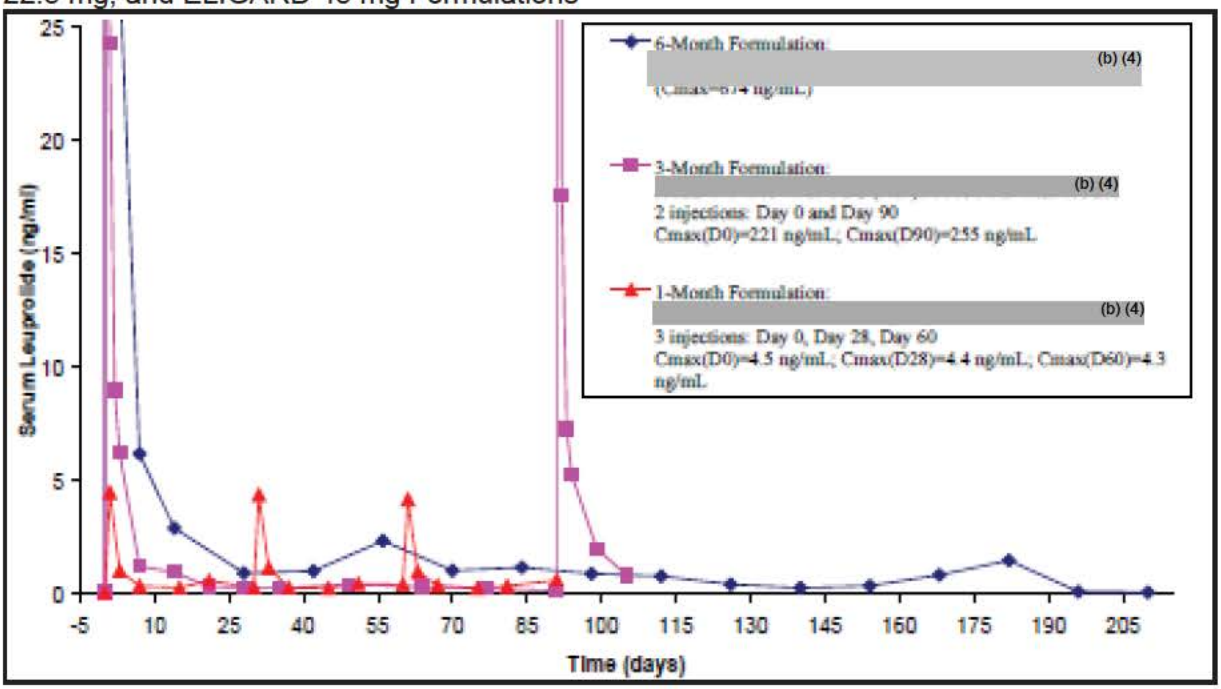
Leuprolide acetate has been in clinical use for over 2 decades and has been administered in both conventional and sustained-release parenteral formulations for the palliative treatment of prostate cancer (as well as other indications). Reports of nonclinical studies in rodents, rabbits, dogs and primates have established the safety of leuprolide acetate after parenteral administration at clinically relevant doses. Aside from effects associated with the pharmacological activity of the drug, no adverse toxicologic effects have been reported in safety pharmacology studies conducted with leuprolide acetate drug formulations.

5 Pharmacokinetics/ADME/Toxicokinetics

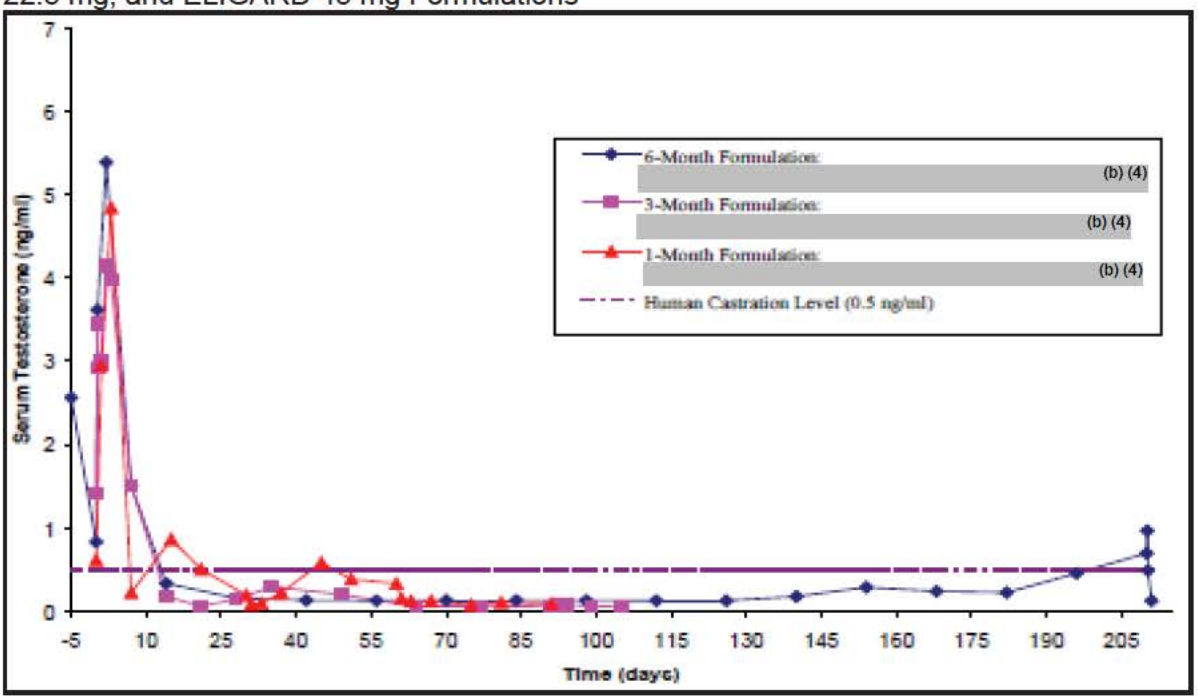
5.1 PK/ADME

The PK/TK and ADME of ELIGARD has been extensively reviewed under NDA 21343 (March 22nd, 2001 - ELIGARD 7.5 mg) and NDA 21731 (March 17th, 2004 - ELIGARD 45 mg). The PK/PD profiles of the ELIGARD 45 mg, ELIGARD 22.5 mg, and ELIGARD 7.5 mg formulations administered to dogs in three studies are depicted below. Similar spikes in serum leuprolide levels are observed after subcutaneous injection, followed by a decline in serum leuprolide levels for the anticipated slow release duration of each formulation. The three ELIGARD formulations suppressed serum testosterone levels at or below human castration levels for one, three or six months, respectively.

Mean Serum Leuprolide Levels After Subcutaneous Injection of ELIGARD 7.5 mg, ELIGARD 22.5 mg, and ELIGARD 45 mg Formulations



Mean Serum Testosterone Levels After Subcutaneous Injection of ELIGARD 7.5 mg, ELIGARD 22.5 mg, and ELIGARD 45 mg Formulations



6 General Toxicology

Tolmar relied on toxicology studies associated with Lupron Depot and the literature for the bulk of the pertinent nonclinical information.

Published Nonclinical Studies for Leuprolide/Leuprolide Sustained Release Formulations

Type of Study	Species	Route	Dose	Duration	Reference
Safety Pharmacology	Mouse, rat, guinea pig, rabbit, cat	SC	1-10 mg/kg leuprolide	Single dose	Kito, et al [a]
Acute Toxicity	Mouse, rat	SC, IP, oral	LD_{50} 5000 mg/kg leuprolide SR formulation (>400 mg/kg as leuprolide)	Single dose	Mikoda, et al [b]
		IM	LD_{50} 2000 mg/kg (>160 mg/kg as leuprolide)		
Repeated Dose Toxicity	Rat, dog	SC	8 or 24 mg/kg/week leuprolide	Single dose monthly for 13 weeks	Chatani, et al [c]
	Mouse, rat, dog, monkey		0.6 mg/kg/day or 0.8 mg/kg leuprolide or leuprolide SR formulation	Single dose monthly for 6, 12 or 24 months	
Antigenicity	Mouse, guinea pig	SC	Leuprolide Copoly (lactic/glycolic) acid (PLGA)	Single dose	Nakai, et al [d]
Subcutaneous Irritation	Rabbits/ KBL:JW/M	SC	3.75 mg/mL/week leuprolide SR formulation	Single dose	Nakai, et al [e]
Fertility and General Reproductive Performance	Rat/ M	SC	Study I: 0.024, 0.24 and 2.4 mg/kg leuprolide	Single dose monthly for 12 and 18 weeks	Ooshima, et al [f]
	Rat/ F		Study II: 0.024, 0.24 and 2.4 mg/kg/4 weeks leuprolide prior to mating	Single dose	
	Rat/ F		Study III: 0.008, 0.024 and 0.08 mg/kg leuprolide on Day 0	Single dose	
Post-Natal Development	Rat /Jcl:Wistar/ F	SC	Leuprolide SR formulation 0.8 and 8 mg/kg (as leuprolide)	Single dose on the day of parturition	Ooshima, et al [g]
Teratology	Rat /Jcl:Wistar/ F	SC	Leuprolide SR formulation 0.0024, 0.008 and 0.24 mg/kg (as leuprolide)	Single dose on Day 6 of pregnancy	Ooshima, et al [h]
	Rabbit/KBL:JW	SC	Leuprolide SR formulation 0.00024, 0.0024, and 0.024 mg/kg (as leuprolide)	Single dose on Day 6 of pregnancy	Ooshima, et al [i]
Micronucleus Test	Mouse/ C3HxSWV	SC	1275, 2750 or 5500 mg/kg leuprolide SR formulation	Single dose	Nakamura, et al [j]
			750, 1500 or 3000 mg/kg leuprolide		
			750 mg/kg/day leuprolide		
In Vitro Cytogenetic Test	CHL cells	In vitro	Leuprolide SR formulation or leuprolide without exogenous metabolic activation system	24 and 48 hours	Fujikawa, et al [k]
			Leuprolide SR formulation or leuprolide in the presence or absence of S9 Mix	6 hours	
ADME	Rat/ Jcl:Wistar/ M and F	SC or IM and SC infusion	100 μg/kg leuprolide	Single dose	Naeshiro, et al [l]
	Beagle dogs/M	SC or IM			

ATRIGEL Delivery System

FENSOLVI is composed of leuprolide acetate and the biodegradable ATRIGEL delivery system consisting of 50:50 Poly (DL-lactide-co-glycolide) COOH/N-methyl-2-pyrrolidone (PLGH/NMP). Sponsor conducted studies of local irritancy and toxicity in rats and local irritancy in rabbits indicate that the ATRIGEL delivery system is well tolerated with findings that were generally comparable to those observed in controls. Histologically, the subcutaneous reaction is consistent with the implantation of a foreign body and the reaction diminishes as the implant degrades. No systemic toxicity was noted following injection of ATRIGEL in rats.

N-Methyl-2-Pyrrolidone (NMP)

Extensive studies of NMP have indicated that this excipient has limited toxicity.

The successful bridging to the literature and the characterization of the NMP and ATRIGEL excipients provided the data needed to support approval and marketing of ELIGARD 45 mg for the palliative treatment of advanced prostate under NDA 021731.

ELIGARD

There were no new pharmacology or toxicology studies submitted with this application and chronic nonclinical toxicity studies of ELIGARD have not been conducted by the Sponsor.

ELIGARD, ATRIGEL and NMP Repeat-Dose Toxicology Studies

BASF 60C0225	Repeat dose	NMP	B6C3F1 Mice	Yes
ATLS-84	Repeat dose	ATRIGEL® Delivery System	SD BR Rat / SC	Yes
		ELIGARD 7.5 mg		
		LUPRON DEPOT® 7.5 mg	SD BR Rat / IM	
ATLS-79	Repeat dose	ATRIGEL® Delivery System	SD BR Rat / SC	Yes
		USP Plastic negative control	SD BR Rat / implant	
HLR 81-95	Repeat dose	NMP	BR Rat / PO in food	Yes
FDRL-6414	Repeat dose	NMP	Beagle Dog	Yes

The longest sub-chronic toxicity study completed to date was a 3-month repeat-dose toxicity study (GLP) in rats that were dosed subcutaneous twice monthly with the ELIGARD 7.5 mg formulation, Lupron Depot 7.5 mg formulation (IM) or Atrigel control (SC). This solitary 3-month repeat-dose toxicity study was deemed sufficient to support the development and approval of all ELIGARD formulations, including the ELIGARD 45 mg formulation for the palliative treatment of prostate cancer, to date.

Rats dosed with the ELIGARD 7.5 mg formulation at 1, 3 or 10 mg/kg (Q2Wk) for 3 months presented with changes in the cellular architecture of the testes and secondary sex organs which are consistent with the compounds mode of action. Localized injection site reactions (bruising, excoriation, scabbing) were noted in rats receiving ELIGARD 7.5 mg or ATRIGEL control, but not in the leuprolide acetate comparator control (Lupron Depot). Hematology and clinical chemistry was not affected by dosing with ELIGARD 7.5 mg and there were no remarkable behavioral changes. The 10 mg/kg (Q2Wk) dose of ELIGARD 7.5 mg in rats represents an exposure margin of 14x to the 45 mg dose (Once/6M) proposed for use in children (20 kg, Ave. BW) with CPP (using an estimated daily dose in animals and humans).

Studies designed to assess the single dose toxicity of FENSOLVI (leuprolide acetate) have not been completed by the Sponsor. Single doses of ELIGARD 45 mg have been administered subcutaneously to rats and dogs in non-GLP complaint pharmacodynamic studies and single dose formulations up to 22.5 mg have been tested in GLP compliant pharmacodynamic studies in dogs. Histological evaluations in these studies were limited to the injection sites.

ELIGARD Pharmacodynamic Studies

Study No.	Study Type	Test Article	Species/Route	GLP
Primary Pharmacodynamic				
ATLS-81	Multiple dose every 30 days	ELIGARD 7.5 mg	Beagle Dog	Yes
ATLS-82	Single dose	ELIGARD 7.5 mg	Beagle Dog / SC	Yes
		LUPRON DEPOT® 7.5 mg	Beagle Dog / IM	
ATLS-87	Multiple dose every 90 days	ELIGARD 22.5 mg	Beagle Dog / SC, IM	Yes
Secondary Pharmacodynamic				
ATRS-170	Single dose	ELIGARD 7.5 mg	SD Rat / SC, bolus	No
ATRS-186	Single dose	ELIGARD 7.5 mg	SD Rat / SC, IM bolus	No
ATRS-180	Single dose	ELIGARD 7.5 mg	Beagle Dog / SC, bolus	No
ATRS-219	Single dose	ELIGARD 7.5 mg	Beagle Dog / SC, bolus	No
		LUPRON DEPOT® 7.5 mg		
ATRS-236	Single dose	ELIGARD 7.5 mg	Beagle Dog / SC, bolus	No
ATRS-277	Single dose	ELIGARD 7.5 mg	Beagle Dog / SC	No
ATRS-233	Single dose	ELIGARD 22.5 mg	Rat / SC	No
ATRS-269	Single dose	ELIGARD 22.5 mg	Rat / SC	No
ATRS-272	Single dose	ELIGARD 22.5 mg	Rat / SC	No
ATRS-289	Single dose	ELIGARD 22.5 mg	Beagle Dog / SC	No
ATRS-400	Single dose	ELIGARD 22.5 mg	Beagle Dog / SC	No
ATRS-444	Single dose	ELIGARD 22.5 mg	Beagle Dog / SC	No
ATRS-445	Single dose	ELIGARD 30 mg	Beagle Dog / SC	No
ATRS-404	Single dose	ELIGARD 45 mg	SD Rat / SC	No
ATRS-499	Single dose	ELIGARD 45 mg	Beagle Dog / SC	No
ATRS-676	Single dose	ELIGARD 45 mg	Beagle Dog / SC	No

7 Genetic Toxicology

The genotoxicity of leuprolide acetate has been extensively reviewed under NDA 21343 (March 22nd, 2001 - ELIGARD 7.5 mg) and NDA 21731 (March 17th, 2004 - ELIGARD 45 mg). Mutagenicity studies have been performed with leuprolide acetate using bacterial and mammalian systems and with ELIGARD 7.5 mg in bacterial systems. These studies provided no evidence of a mutagenic potential. The excipient *N*-Methyl-2-pyrrolidone was not found to be genotoxic in various *in vitro* and *in vivo* studies.

ELIGARD and NMP Genotoxicity Studies

Study No.	Study Type	Test Article	Species/Route	GLP
Genotoxicity In Vitro				
ATLS-85	Mutation	ELIGARD 7.5 mg	Salmonella typhimurium (five strains)	Yes
HLR 677-76	Mutation	NMP	Mouse lymphoma cell line L5178Y	No

8 Carcinogenicity

The carcinogenic potential of FENSOLVI has not been assessed directly. The Sponsor relies on the established carcinogenicity data of leuprolide in the literature (Lupron, TAP-144 non-SR, Chatani et. al., 1990) that was deemed adequate to support the approval and marketing of previous leuprolide applications including the RLD, Lupron Depot PED.

Two-year carcinogenicity studies were conducted with Lupron (TAP-144 – non-sustained release formulation) in rats and mice. In rats, a dose-related increase of benign pituitary hyperplasia and benign pituitary adenomas was noted at 24 months when the drug was administered subcutaneously at high daily doses (0.6 to 4 mg/kg). There was a significant but non-dose related increase of pancreatic islet-cell adenomas in females and of testicular interstitial cell adenomas in males (highest incidence in the low dose group). Lupron did not induce tumors or pituitary abnormalities in mice dosed as high as 60 mg/kg for two years.

9 Reproductive and Developmental Toxicology

The reproductive and developmental toxicology of FENSOLVI has not been assessed directly. The Sponsor relies on the reproductive and developmental data associated with leuprolide in the literature (Lupron Depot, TAP-144-SR, Ooshima et. al.,1990) that has been deemed adequate to support the approval and marketing of previous leuprolide NDAs including the RLD, Lupron Depot PED.

Reproduction and teratology studies utilizing Lupron Depot (TAP-144-SR), a leuprolide acetate formulation with sustained release characteristics similar to ELIGARD, indicated that the observed toxicological effects of leuprolide acetate are related to the pharmacological actions of the compound. Major fetal malformations were observed in developmental and reproductive toxicology studies in rabbits after a single administration of the monthly formulation of leuprolide acetate (TAP-144-SR) on day 6 of pregnancy at doses of 0.00024, 0.0024, and 0.024 mg/kg (approximately 1/3255 to 1/33 the human dose based on the body surface area of a 20 kg child and using an estimated daily dose in animals and humans). Since a depot formulation was utilized in the study, a sustained exposure to leuprolide was expected throughout the period of organogenesis and to the end of gestation. Similar studies in rats did not demonstrate an increase in fetal malformations, however, there was increased fetal mortality and decreased fetal weights with the two higher doses of the monthly formulation of leuprolide acetate in rabbits and with the highest dose (0.024 mg/kg) in rats.

Fertility studies utilizing male rats dosed once every 4 weeks for three doses prior to mating, demonstrated dose-related reversible atrophy of the testes or accessory sex organs, and a decrease in LH, FSH and testosterone levels. A reversible decrease in copulation and implantation sites was noted at the HD and no effects on the fetuses were observed. Female (HD) rats dosed for 4 weeks prior to mating, presented with an interruption of the estrus cycle and decreased vaginal size. Weights of the ovaries and uterus were decreased. Following mating, corpora lutea and the number of implantation sites were decreased at all doses. No abnormal development was noted in the fetuses. The literature reports that Lupron Depot (TAP-144-SR) was not teratogenic in either rats or rabbits. In a perinatal study, the administration of Lupron Depot prior to delivery altered sex organ weights, but there were no adverse effects on the fetuses, including fetal sex organs weights.

Note: Historically, impairment of fertility information has been excluded from ELIGARD labels for treatment of advanced prostate cancer, presumably because most such patients have been castrated. However, such information is pertinent to an adolescent CPP population and should be included in the FENSOLVI drug label if the indication is approved. This information is available in the literature and is also described in the Lupron Depot PED drug product label.

The Pharm/Tox reviewer of IND 64779 (ELIGARD 45 mg - palliative treatment of advanced prostate cancer - NDA 021731) expressed concern that the safety of NMP had not been adequately assessed with regards to its teratogenic potential and may require further toxicity testing for benign indications (July 2002).

The Sponsor selected studies below suggest that the reproductive and developmental toxicity of NMP is generally confined to dose levels that induced overt maternal toxicity. While this may be the case for these specific oral and dermal studies, rat inhalation studies of NMP have reveled skeletal and cognitive changes in fetuses derived from dams that lacked any signs of overt maternal toxicity. Teratogenic effects have been observed in rabbits where marked embryo-toxicity was present and in published mouse studies (Germany). DART studies utilizing the subcutaneous route of administration (pertinent ROA) have not been reported.

NMP DART Studies (Sponsor Selected)

Study No.	Study Type	Test Article	Species/Route	GLP
(b) (4) 136534	Reproductive	NMP	BR Rat / PO (gavage)	Yes
5210	Reproductive	NMP	BR Rat / dermal	Yes
5161	Reproductive	NMP	BR Rat / dermal	Yes
70R0056	Reproductive	NMP	Wistar Rat / PO in food	Yes
236535	Reproductive	NMP	BR Rat / PO in food	Yes
(b) (4) 97-4106	Reproductive	NMP	BR Rat / PO in food	Yes

10 Special Toxicology Studies

Local Tolerance

The local tolerance of subcutaneously administered ELIGARD was assessed in rabbits (up to 22.5 mg formulation) and rats (up to 7.5 mg formulation) in GLP compliant studies. Non-GLP compliant local tolerance studies have been completed in pigs (up to 30 mg formulation) and rats (up to 45 mg formulation) utilizing the subcutaneous route of administration. ELIGARD induces irritation at the cellular level that tends to normalize in the absence of dosing a finding consistent with the subcutaneous implantation of biodegradable polymers.

ELIGARD and ATRIGEL Local Tolerance Studies

Study No.	Study Type	Test Article	Species/Route	GLP
Local Tolerance				
ATLS-86	Local tolerance	ATRIGEL® Delivery System ELIGARD 7.5 mg	Hsd:SD Rat / SC	Yes
ATRS-226	Local tolerance	ELIGARD 7.5 mg	SD Rat / SC	No
ATRS-237	Local tolerance	ELIGARD 7.5 mg	SD Rat / SC	No
ATRS-189	Local tolerance	ATRIGEL® Delivery System USP Plastic negative control	SD Rat / SC SD Rat / implant	Yes
ATLS-83	Local tolerance	ELIGARD 7.5 mg USP Plastic negative control	NZW Rabbit / SC NZW Rabbit / implant	Yes
ATLS-78	Local tolerance	ATRIGEL® Delivery System USP Plastic negative control	NZW Rabbit / SC NZW Rabbit / implant	Yes
ATRS-239	Single dose, local tolerance	ELIGARD 7.5 mg	Beagle Dog	No
ATLS-88	Single dose, local tolerance	ELIGARD 22.5 mg / USP Plastic negative control	NZW Rabbit / SC	Yes
ATRS-364	Multiple dose	ELIGARD 30 mg	Pig	No
ATRS-465	Local tolerance	ELIGARD 45 mg	SD Rat / SC	No
ATRS-486	Local tolerance	ELIGARD 45 mg	SD Rat / SC	No
ATRS-628	Local tolerance	ELIGARD 45 mg	SD Rat / SC	No

11 Integrated Summary and Safety Evaluation

The Sponsor relies on Lupron Depot PED (NDA 20263), Eligard (NDA 21731),and the literature for the pertinent nonclinical information. The acceptable quality assessment of the API in Fensolvi relative to the API in these NDAs supports the use of the same nonclinical information in sections 8 and 13 of the drug label for Fensolvi.

The studies conducted with the ATRIGEL delivery system and NMP indicate that these excipients represent a minimal risk to juvenile patients at the proposed dose and duration.

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/s/

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