CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-088

PHARMACOLOGY REVIEW(S)

FEB - 7 2000

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA:

KEY WORDS: Viadur, Leuprolide acetate, GnRH analog, Prostate cancer

Reviewer Name: Krishan L. Raheja

Division Name: DRUDP

HFD#: 580

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Review number: Original submission

IND/NDA number: NDA # 21-088

Serial number/date/type of submission: Original submission/4-30-1999/NDA

Information to sponsor: Yes (*) No ( )

Sponsor (or agent): ALZA Corporation, Palo Alto, CA

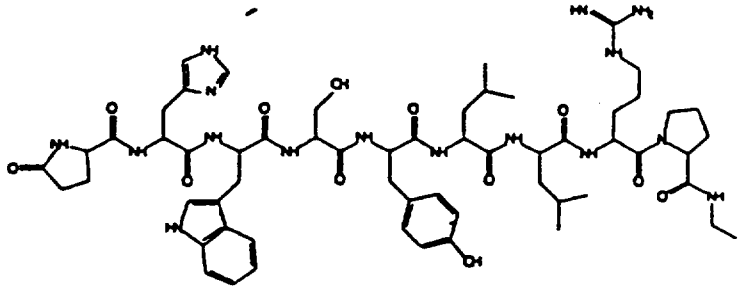
Manufacturer for drug substance:

Drug:

Code Name: CPC-2 or TDC-13
Generic Name: Duros Leuprolide Implant
Trade Name: Viadur
Chemical Name of drug substance: 5-Oxo-L-propyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-Leucyl-L-arginyl-N-ethyl-L-prolinamide acetate (salt)
CAS Registry Number: 74381-53-6
Molecular Formula/ Molecular Weight: $C_{59}H_{84}N_{16}O_{12}$/1209.1

Structure:

Structural formula (free base):



pGlu-His-Trp-Ser-Tyr-D-Leu-Leu-Arg-Pro-N-EthylAmide

Relevant INDs/NDAs/DMFs: .

Drug Class: GnRH agonist

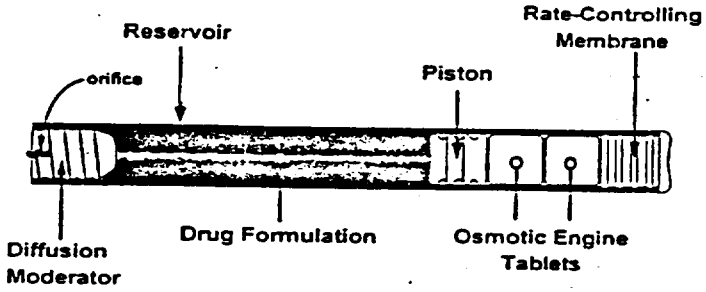
Indication: For the palliative treatment of advanced prostate cancer

Clinical formulation: Viadur (leuprolide acetate) implant is a nonbiodegradable, osmotically driven miniaturized implant to deliver leuprolide acetate continuously over a period of one year. The system contains 65 mg of the leuprolide and each unit is designed to deliver a nominal dose of about 0.12 mg/day for 12 months (about 0.0021 mg/kg/day for a 70 kg patient).

Viadur contains leuprolide in dimethyl sulfoxide (DMSO). The drug loading is 37 weight percent of leuprolide free base in DMSO.

A 4-mm x 45-mm titanium alloy reservoir houses a polyurethane rate limiting membrane, an elastomeric piston, and a polyethylene diffusion moderator as shown in figure below. The reservoir also contains the osmotic tablets, which are composed of sodium chloride, sodium carboxymethyl cellulose (a gelling agent), povidone (tablet granulation aid), magnesium stearate (tablet lubricant), and sterile water for injection. Polyethylene glycol ( ) fills the space between the osmotic tablets and the reservoir.

DUROS Leuprolide Implant Structure



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ON ORIGINAL

DUROS Leuprolide Implant Formulation Composition

DUROS Component	Material	Amount
Drug formulation		
	Leuprolide acetate	72 mg
	Dimethyl sulfoxide	
Osmotic engine		
Tablet	Sodium chloride, USP	
	Magnesium stearate, NF	
	Polyvinylpyrrolidone (Povidone),USP	
	Carboxymethyl cellulose Na	
	Sterile water for injection	
Compartment filler	Polyethylene glycol	
Reservoir	Titanium alloy,	
Membrane rate limiting	Polyurethane thermoplastic Elastomer,	
Diffusion moderator	High density polyethylene	
Piston	Thermoplastic elastomer,	
Piston lubricant	Silicone med Fluid (SMF)	

mm

Route of administration: The implant is inserted subcutaneously in the inner aspect of the upper arm.

Proposed clinical protocol or Use: The implant will be used for the palliative treatment of prostate cancer

Previous clinical experience with leuprolide acetate: There is an extensive clinical safety efficacy data available not only for the palliative treatment of prostate cancer, which is the indication for the DUROS Leuprolide Implant, but also for its use in the treatment of endometriosis, uterine fibroids and precocious puberty.

To establish the safety and efficacy of DUROS Leuprolide Implant, the sponsor has conducted the following 2 clinical studies with the proposed formulation:

1. A dose-ranging study evaluating the safety and efficacy of one or two DUROS Leuprolide Implants (Study C-96-011)
2. The confirmatory study evaluating the safety and efficacy of the one-implant dose (Study C-97-010).

These studies were conducted in 2 phases with a 1-year Treatment Phase followed by a 1-year Safety Extension Phase. After the first year treatment, implant(s) were extracted and replaced with a new implant. Data submitted includes the Treatment Phase through reinsertion for both studies and also from the first 2 months following reinsertion for study C-96-011.

The safety evaluation of the DUROS Leuprolide Implant led to the following conclusions:

1. The implant was well tolerated throughout the 1-year implantation period. It was also well tolerated in the 2-month after reimplantation.
2. No serious adverse effect (AE) was reported to be related to the treatment.
3. The majority of the systemic AEs were those associated with the physiologic effects of testosterone suppression.
4. Most application site reactions were secondary to the insertion or reinsertion procedures, and were mild, transient, and resolved rapidly, usually within 2 weeks of implant insertion.
5. There was no evidence of the formation of antibodies to leuprolide.

Based on data from a total of 131 patients, it was concluded that DUROS Leuprolide Implant demonstrated its safety, efficacy, and clinical utility in the palliative treatment of advanced prostate cancer.

Disclaimer -- use of sponsor's material

Introduction and drug history: Leuprolide acetate is a synthetic nonapeptide analog of the naturally occurring gonadotropin-releasing hormone (GnRH or LH-RH). The analog possesses 80-100 times greater potency than the native GnRH.

Daily injection and depot formulations of leuprolide acetate have been the mainstays in the hormone ablation therapy regimens since the introduction of this active substance to the market in the United States in 1985. Since then leuprolide formulations have been launched in 36 countries.
Lupron as leuprolide acetate for injection and Lupron Depot as leuprolide acetate for depot suspension are approved for various indications. Lupron injection is approved for the palliative treatment of the advanced prostate cancer and for the treatment of children with central precocious puberty. Lupron Depots 3.75 is approved for the treatment of endometriosis, Lupron Depot 7.5 mg and Lupron Depot-3 month 22.5 mg for the palliative treatment of prostate cancer, and Lupron Depot-PED 7.5, 11.25 and 15 mg for the treatment of children with central precocious puberty.
The proposed dosage form is an extension of ALZA Corporation's osmotic pump technique examplified by the ALZET osmotic pump and the Veterinary Implantable Therapeutic System (VITS)

Clinical benefits of DUROS Leuprolide Implant: Although the safety and efficacy profiles of this product are reported to be generally comparable to those reported in the literature for the existing 1-month, 3-month, and 4-month Lupron Depot formulations, the sponsor has claimed that the DUROS Implant has the potential to provide additional benefits, including the following:

1. Maintenance of continuous therapeutic levels of serum leuprolide for one year after a single administration of the implant.
2. Minimized risk of noncompliance and thus of the disease flare.
3. Maintenance of adequate testosterone suppression for one year.
4. No observed testosterone escape during the treatment interval.
5. No "acute-on-chronic" phenomenon with the insertion of a new implant.
6. Ability to discontinue the therapy through implant removal if desired.

Based on the above suggested benefits, the sponsor implied that DUROS Leuprolide Implant represents an important advance over existing standard of care for patients with advanced prostate cancer.

Studies reviewed within this submission: Studies reviewed within this submission include sponsor's conducted chronic toxicity studies with DUROS Leuprolide Implants as well as biocompatability studies with DUROS system components. Also biological testing, cytotoxicity testing and genotoxicity studies conducted with DUROS system components are reviewed. Some of these studies have been reviewed

Studies <u>not</u> reviewed within this submission: ADME and toxicology studies for leuprolide acetate (i.e., acute toxicity, subchronic toxicity in mice, rats, dogs and monkeys; chronic toxicity in mice, rats, dogs and monkeys; carcinogenicity in mice and rats; developmental and reproductive toxicity; and genotoxicity) are not reviewed within this submission. Instead these studies have been supported by reference to TAP Holdings NDAs for Lupron (listed below) as well as to published literature for which appropriate citations and copies of publications have been provided.
TAP Holdings NDAs referred by the sponsor to support ADME and toxicology for leuprolide acetate include the following:

NDA #	Date approve	Drug name	Indications
19-010	4-9-1985	Lupron Injection	Treatment of prostate cancer
19-732	1-26-198	Lupron Depot Injection	Palliative treatment of advanced prostate cancer
20-011	10-22-1990	Lupron Depot 3.75 mg	Treatment of endometriosis
20-263	4-16-1993	Lupron Depot Pediatric kit	Treatment of children with central precocious puberty

19-943	3-30-1995	Lupron Depot Injection	Treatment of leiomyoma uteri (Uterine fibroids)
20-517	12-22-1995	Lupron Depot-4 month 30 mg	Palliative treatment of advanced prostate cancer
20-708	3-7-1997	Lupron Depot 3 month 11.25 mg	Treatment of endometriosis

PHARMACOLOGY:

Leuprolide acetate, a Gn-RH agonist, acts as a potent inhibitor of the gonadotropin secretion when given continuously in therapeutic doses. In both the animals and humans after an initial stimulation, chronic administration results in suppression of the ovarian and testicular steroidogenesis. This effect is due to the down regulation (i.e. desensitization) of the pituitary gonadotropin receptors in humans and monkeys. In the male rats, there is a direct testicular effect, resulting in the loss of the testicular LH receptors.

In humans, administration of leuprolide acetate results in an initial increase in circulating levels of leutinizing hormone (LH) and follicle-stimulating hormone (FSH), leading to a transient increase in the concentrations of the gonadal steroids (testosterone and dihydrotestosterone in the males and estrone and estradiol in the premenopausal women). However, continuous administration of leuprolide acetate results in decreased levels of LH and FSH. Thus in the males, testosterone is reduced to castrate levels and in the premenopausal females, estrogens are reduced to postmenopausal levels.

The decrease in the sex hormones results in the inhibition of the growth of the sex hormone dependent tumors as well as atrophy of the reproductive organs. Palliative treatment of prostate cancer is achieved by the maintenance of castrate levels of testosterone in men with prostate cancer. The effects of leuprolide acetate are reversible upon discontinuation of the drug treatment.

Mechanism of Action: Leuprolide acetate acts as an inhibitor of the gonadotropins secretion due to the gonadotropin receptor desensitization when given continuously with resultant inhibition of the gonadal steroidogenesis.

Drug Activity Related to Proposed Indication: The general effect of chronic leuprolide acetate treatment is the creation of a state of hypogonadism.

Summary of pharmacology: Both in the animals and humans, administration of leuprolide acetate results in an initial increase in the circulating levels of LH and FSH, leading to transient increase in the levels of gonadal steroids. However, continuous administration results in desensitization of pituitary gonadotropins receptors, with a decrease in the levels of LH and FSH, resulting in hypogonadism.

SAFETY PHARMACOLOGY: Referred to the FDA's approved TAP Holdings NDAs and to published literature.

PHARMACOKINETICS/TOXICOKINETICS: Referred to the FDA's approved TAP Holdings NDAs and to published literature.

The only pharmacokinetics data available with the use of DUROS Leuprolide Implant is from a 24-week toxicity study in rats (Bio-95-B025-4904) and 60-week toxicity in dogs (Bio-95-B046-4904). These studies have been reviewed. These studies are summarized below:

In the rat study, following 5 treatment groups were used:

1. Prototype DUROS Leuprolide with titanium reservoir
2. Prototype DUROS Placebo with titanium reservoir
3. Prototype DUROS Leuprolide with HDPE reservoir
4. Prototype DUROS Placebo with HDPE reservoir
5. HDPE control rod

The target dose of leuprolide was about 125 ug/day. Based on rat's body weight of 0.3 kg, the nominal leuprolide dose was calculated to be approximately 415 ug/kg/day. Serum testosterone and leuprolide levels at treatment weeks 6, 12 and 24 are shown in table below:

Table 1. **Serum leuprolide and testosterone levels in rats**

	Testosterone (ng/dl) weeks			Leuprolide (ng/ml) weeks		
Group #	6	12	24	6	12	24
1	3-44	5-93	44-58	2.6-33.4	0.8-15.8	2.8-5.7
2	36-368	27-143	49-206	0	0	0
3	14-84	6-64	41-132	6.4-21.0	3.3-10.1	0.3-17.1
4	30-116	49-86	43-86	0	0	0
5	34-197	40-108	40-108			

There were 14-15 male SD rats in groups 1-4 and 9 in group 5. One test and one placebo article was implanted sc in each rat. 4-6 rats were sacrificed at 6, 12 and 24 weeks post-implantation. Just prior to sacrifice blood was collected for serum testosterone and leuprolide determination.

Serum testosterone concentrations were markedly decreased in 1 of 5 DUROS leuprolide HDPE treated rats at 6 and 12 weeks and in 3 of 6 DUROS leuprolide titanium treated rats at 6 weeks postimplantation and 1 of 5 rats 12 weeks postimplantation. No decrease was seen at 24 weeks.

Serum leuprolide concentrations were very variable in both DUROS implant treated groups. There was no correlation between high serum leuprolide concentrations and low serum testosterone concentrations.

Based on these data, rat model was considered to be not an appropriate species for the investigation of testosterone suppression by leuprolide.

Table 2. **Study design for 60-week dog toxicity study**

Group	# of dogs	Test article	Route of Administration	# of dogs(x/x) duration in life (wks)
1	4	None	Sham surgery	(4/4) 60
2	4	Lupron Depot	Monthly IM	(4/4) 60
3	4	DUROS (aqueous formulation)	SC implant	(4/4) 22
4	6	DUROS (aqueous formulaiton)	SC implant	(2/6) 22 (4/6) 22 + 15 wk recovery
5	6	DUROS (DMSO formulation)	SC implant	(6/6) 60 [52 + 8 wk reimplantation]

The dose for both the Lupron Depot and DUROS formulation groups was 125 ug/day.

DUROS Leuprolide Implants provided continuous delivery of leuprolide throughout the course of the study. Groups mean serum concentrations for dogs receiving DUROS Leuprolide Implants (DMSO formulation) ranged from 0.71 to 9.63 ng/ml throughout the course of the study. However, over 86% of the group mean leuprolide concentrations was between 1.15-4.00 ng/ml. Only 3/513 (0.6%) of the analyzed samples were below the limit of quantification. A decrease in serum level of leuprolide was not observed after removal of the implants and reinsertion of new DUROS implants on Day 365.

For dogs receiving Lupron Depot, serum leuprolide concentrations ranged from below the limit of detection to 0.62 ng/ml throughout the course of the study. Of the 270 analyzed samples, 103 (38%) had concentrations below the limit of detection. Over 30% of the analyzed samples from dogs receiving 3.75 mg Lupron Depot, were below the limit of detection during the 24 hour sampling period, when leuprolide was detectable in all blood samples from dogs which received DUROS Leuprolide Implants.

Serum testosterone concentrations were decreased to castrate levels (below 50 ng/dl) by Day 29 of treatment and below the limit of quantification by Day 43 in the DUROS Leuprolide Implant (DMSO formulation) group and below the limit of detection by Day 11 in the Lupron Depot group.

Dog study results thus demonstrated that as in the rats, there was no correlation between the serum leuprolide levels and testosterone suppression.

Viadur absorption in humans: After insertion of Viadur, onset of the drug delivery was rapid, with mean leuprolide concentrations of 16.9 ng/ml at 4 hours and 2.4 ng/ml at 24 hours. Thereafter, leuprolide was released at a constant rate with mean serum leuprolide concentrations being maintained at 0.9 ng/ml (0.3-3.1 ng/ml) for one year. Upon removal and insertion of a new Viadur at 12 months, steady-state leuprolide concentrations were maintained.

In a study comparing one Viadur implant to two Viadur implants, mean serum leuprolide concentrations were reported to be proportional to dose.

It was stated that following the initial insertion, mean serum testosterone concentrations increased 50% or more by Day 3 in majority of the patients, followed by rapid decrease to baseline in all patients. Castrate levels of serum testosterone (<50 ng/dl) were achieved by 99.1% of evaluable patients between weeks 2 and 4. Once serum testosterone suppression was achieved, no escape from suppression was observed in any patient.

Leuprolide distribution, metabolism and excretion were referred to Lupron labeling.

TOXICOLOGY:

General Comments: Toxicity of leuprolide acetate has been extensively investigated and published. Leuprolide acetate has been approved by the FDA for many indications under various TAP Holdings NDAs.

Sponsor has referred all nonclinical toxicology for leuprolide acetate (i.e., acute toxicity, subchronic toxicity in mice, dogs and monkeys; chronic toxicity in mice, rats, dogs and monkeys; carcinogenicity in mice and rats; developmental and reproductive toxicity; and genotoxicity) to TAP Holdings NDAs for Lupron as well as to published literature.

Sponsor however, has conducted chronic toxicity studies with DUROS Leuprolide Implants as well as biocompatability studies with DUROS system components. Also biological testing, cytotoxicity testing and genotoxicity studies were conducted with DUROS system components. Some of these studies have been reviewed under

The following toxicity studies were conducted by the sponsor:

Study Title: Evaluation of in vivo performance and local tissue response of DUROS Leuprolide in rats (32 week implantation in rats).

Study No: BIO-95-B025-4904
Vol #/page #: 1.40/6
Conducting laboratory and location: Toxicology Laboratory, ALZA Corporation, Palo Alto, CA
Date of study initiation: 7-28-1995
GLP compliance: Non-GLP
QA- Report: Yes () No (*)
Methods:
Dosing:

- species/strain: rats/Sprague Dawley
- #/sex/group or time point: male
- age: adult
- weight: at least 250 g
- satellite groups used for toxicokinetics or recovery: none
- dosage groups in administered units: As described under ADME on page
- route, form, volume, and infusion rate: Subcutaneous, DUROS Implants, 0.3 ul/day

Drug, lot#, radiolabel, and % purity: N/A
Formulation/vehicle: 60% propylene glycol/27% water/3% sodium carboxymethylcellulose
Observations and times:

- Clinical signs: 2 hours after implantation and then daily for 7 days
- Body weights: pre-implantation and then weekly
- Food consumption: N/A
- Ophthalmoscopy:
  Hematology: weeks 6 and 12
- Clinical chemistry: weeks 6 and 12
- Gross pathology: 6, 12 and 24 weeks
  Histopathology: 6, 12 and 24 weeks (implantation site)
- Toxicokinetics: 6, 12 and 24 weeks
- Other: serum testosterone at weeks 6, 12 and 24

Results:

- Clinical signs: No deaths or morbidity. HDPE reservoirs did not maintain their
- integrity and 3 of 4 were split at the membrane end by 6 weeks.
- Body weights: No treatment effect
- Hematology: No treatment related changes
- Clinical chemistry: No treatment related changes
- Gross pathology: as shown in table below
- Histopathology: as shown in table below
- Toxicokinetics: as given in table 1 under ADME on page

Implant site irritation was recorded both macroscopically and microscopically. Shown in table below are total macroscopic score (capsule + vascularity + fluid) and microscopic score for groups 1-5 for the 6, 12 and 24 week explants:

Table 3. **Effect of leuprolide implants in rats on skin irritation**

	Macroscopic			Microscopic		
Group	6 week	12 week	24 week	6 week	12 week	24 week
1	3.5	2.6	2.0	4.3	2.2	4.5
2	3.6	2.4	2.4	4.2	3.8	3.4
3	3.8	4.4	3.4	7.0	7.6	6.0
4	4.3	4.7	3.8	8.8	11.5	6.6
5	3.3	2.7	2.7	3.3	4.0	5.0

Group 1=dDuros leuprolide with titanium reservoir, group 2=Duros Placebo with titanium reservoir, group 3=Duros leuprolide with HDPE reservoir, group 4=Duros Placebo with HDPE reservoir and group 5= HDPE control rod

For macroscopic evaluation, grade score scale was 0-4. Thus total macroscopic score ranged from 0-12 for capsule + vascularity + fluid. Scoring was 0-1.0 as minimal, 1.1-4.0 as mild, 4.1-7.0 as moderate, 7.1-10.0 as severe and 10.1-12.0 as extreme.

For microscopic evaluation also grade score was 0-4. Inflammation parameters checked were polymorphonuclear lymphocytes, plasma cells, macrophages, giant cells, and fibroplasia, fibrosis, necrosis and mineralization. For microscopic evaluation (test – control) scores of 1-10= mild irritation, 11-25= moderate and >26= marked irritation.

Thus macroscopic response to HDPE reservoir was mild to moderate and with titanium reservoir mild. Similar trend was seen on microscopic evaluation. Reaction was more at 12 weeks and then reduced by 24 weeks. No reaction was seen at sham sites.

As pointed out under ADME, there was no correlation between high serum leuprolide concentrations and low serum testosterone concentrations, suggesting rat not being an appropriate model for testosterone suppression by leuprolide.

Inconsistent delivery observed in the in vivo and in vitro pumping comparisons was suggested to be due to formulation stiffening, membrane protrusion and HDPE reservoir splitting. In spite of that in vivo/in vitro delivery correlated to within about 20% for implants with titanium reservoir at 6 and 12 weeks.

Overall Toxicology Summary: Both DUROS leuprolide implants with titanium and HDPE reservoirs were well tolerated. No significant macroscopic or microscopic reaction was reported at the implantation sites.

Addendum list: Copies of reviews of the original

Study title: Evaluation of in vivo performance and local tissue response of DUROS Leuprolide in dogs.

Study No. BIO-95-B046-4904
Vol #/page #: 1:40/209
Conducting laboratory and location:
Date of study initiation: 1-23-96
Date of termination: The duration of the study was originally designed to be 13 weeks. However, because of the favorable DUROS leuprolide implant delivery results, the study was extended to 155 days for implant delivering the water/leuprolide formulation and to 60 weeks for implants delivering the DMSO/leuprolide formulation. After 52 weeks these dogs had their DUROS implants removed and replaced with new leuprolide implants from clinical production run for an additional 8 weeks.
GLP compliance: Non-GLP
QA-Report: Yes ( ) No (*)

Methods:

Dosing:
Species/strain: Dogs/Beagle
#/sex /group or time point: as shown in table on page
age: at least 9 month
weight: N/A
satellite groups used for toxicokinetic or recovery: see table on page
dosage groups in administered units: as described under ADME. Sham operated dogs and dogs receiving injections of Lupron Depot 3.75 mg every 28 days served as controls.

route, form, volume, and infusion rate: subcutaneous, DUROS implants, 0.4 ul/day, 125 ug/day
Drug lot#, radiolabel, and % purity: N/A
Formulations: DUROS TDC-13A-40% Leuprolide acetate/60% water
DUROS TDC-13B-40% Leuprolide acetate/60% DMSO
Positive control article-Lupron Depot 3.75 mg TAP Pharmaceuticals
Observations and times:
Clinical signs: twice daily for mortality and moribundity; once daily for cageside clinical signs of toxicity, physical exam every week.
Body weight: prior to treatment and then weekly
Clinical pathology: Hamatology and clinical chemistry: Day –4 (prior to initiation), 364 and 420 (for groups 1,2, and 5 animals).
Gross pathology: All animals necropsied (groups 1, 2 and 5). All organs examined.
Organ weights: adrenal glands, brain, heart, kidneys, liver, lungs, ituitary galns, prostate gland, spleen, salivary gland, testes with epididymides, thymus and thryroid/parathyroid gland. Organ to terminalb.wt and organ/brain wt ratios calculated.
Histopathology: All required tissues preserved in 10% neutral buffered formalin.
Toxicokinetics: as under pharmacokinetics page 8 .

Results:

Mortality and clinical signs: All animals survived to scheduled termination. Compared to controls, testicles in animals of groups 2 and 5 smaller and atrophic
Body weight: no treatment-related effect
Clinical pathology: Values prior to start of study and on days 364 and 420 did not demonstrate any treatment effect.
Testosterone levels: as given under ADME on page
Leuprolide levels: as given under ADME on page

Gross pathology: At termination other than atrophy of testicles and prostate gland, no gross findings associated with the test material were reported.
Organ weights: mean weights of testes and prostate gland were significantly lower in treated groups 2 and 5 when compared to control group 1.
Histopathology: atrophy of the testes, epididymides and prostate glands.
Macroscopic evaluation of implant sites: All DUROS implants caused mild tissue reactions. DUROS leuprolide implants with aqueous formulation excised on Day 155 resulted in mild encapsulation with none to minimal increase in vascularity, and fluid accumulation. DUROS leuprolide implants containing DMSO/leuprolide formulations excised on Day 365, caused mild tissue reaction. All implant sites showed mild encapsulation and minimal increases in vascularity with no fluid accumulation. Implants excised on Day 421 (8 weeks after reimplantation), had mild to moderate encapsulation and none to minimal increases in vascularity with no fluid accumulation.
Microscopic evaluation of implant sites: Implant site reaction with DUROS leuprolide implant was mild to moderate. Five out of six implant sites from DUROS leuprolide implants with aqueous formulation, excised on Day 155 showed fibrous tissue formation associated with slight to moderate degree of fibroblastic proliferation. No histological abnormalities in sites of implants removed on Day 155 were seen after healing process on Day 286. The tissue around implants removed on Day 365 showed mild to focally severe fibrotic wall with minimal to severe inflammatory reaction luminally. The inflammatory reaction consisted of mostly histiocytes, with a mean score of 1.3 to 17.0 out of maximum site score of 56 i.e, mild to moderate reaction. Eight weeks after re-implantation on excision Day 421, there was mild to moderate compacted fobrosis surrounding a minimal to focally moderate inflammatory reaction

around the lumen. The mean inflammatory score was mild to moderate and ranged from 7.3 to 14.3 out of 56. Lupron Depot sites were not evaluated.

Leuprolide antibody assay: An enzyme-linked immunoabsorbent assay (ELISA) specific for canine IgG and IgM was used to evaluate serum samples for the presence of anti-leuprolide antibodies. For IgG, one sham dose was always positive during the 420-day study duration. Two DUROS leuprolide dogs were positive at one point. No positive values were observed for Lupron Depot treated grouop. For IgM, one sham treated dog exhibited positive value and none for DUROS leuprolide or Lupron Depot groups.
Summary: Serum samples from DUROS leuprolide implant or Lupron Depot treated dogs did not significantly differ from sham-treated dogs in terms of the presence of anti-leuprolide antibodies.

Study Title: An implant/explant study of DUROS implants with titanium and HDPE reservoirs in swine.

Study No. BIO-95-B026-4904
Vol #/Page #: 1.42/220
Conducting laboratory and location:
Date of study initiation: 8-15-1995
GLP compliance: GLP
QA Report: Yes
Methods:
Dosing:

Species: miniature swine/Hanford
#/sex/group or time point: 2 females/g
Satellite groups used for toxicokinetics or recovery: groups 2 and 4 used for recovery
Dosage groups in administered units: see study design below
Route, form, volume, infusion rate: subcutaneous, DUROS Implants (titanium reservoir
Drug lot #, radiolabel, and purity: N/A
Formulation/vehicle: vehicle formulation 1% sodium carboxymethylcellulose in 0.9% saline
Experimental design: was as follows:

Table 4. **Experimental design of swine toxicity study**

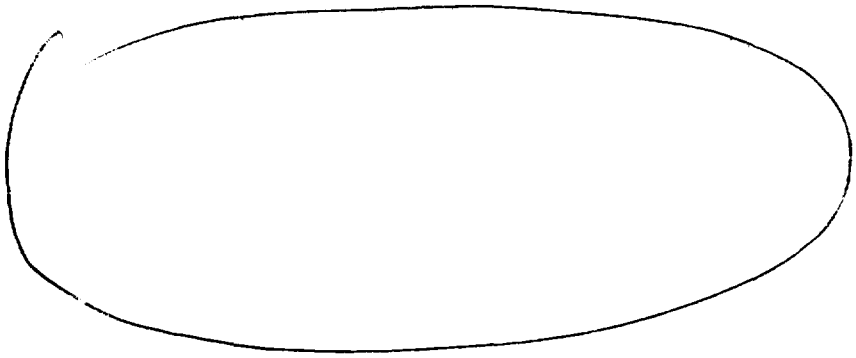
Group No	# of pigs	# implants/pig	Duration of implantation	Euthanasia (# of wks post implantation
1	2	6	4	4
2	2	6	4	7
3	2	6	12	12
4	2	6	12	15

Two different prototypes of DUROS implants (non-drug containing) i.e., 3 HDPE and 3 titanium DUROS implants were implanted SC in each pig. Each pig also had 2 "sham" implants.
After 4 weeks, group 1 and 2 had implants removed. Pigs in group 1 were euthanized immediately, while those in group 2 were allowed to recover for 3 weeks post-explantation and then euthanized. Implants in group 3 and 4 were removed after 12 weeks and again group 3 pigs were euthanized immediately while those of group 4 were euthanized 3 weeks later.
Results: The DUROS implants were easy to implant and explant. There was minimal to moderate excapsulation of all DUROS implants. For vascularity and fluid, all sites were scored zero. Histological

examination showed a minimal response to all DUROS implants and both types of implants had a similar histological score. There was a minimal migration of the implants, ranging from none to 1 cm. The sites of the animals that were allowed to recover, healed very well. No other adverse effects were reported. Summary: Based on the above macroscopic and microscopic observations, the DUROS implants were considered very biocompatable in the swine model.

Study title: DUROS implant technology piston, diffusion moderator, reservoir, and rate-controlling membrane: 90-day subcutaneous biocompatability study in beagle dogs.

Study No.: TR-98-5904-012.
vol.#/ page #: 1.43/1
Conducting laboratory and location:
Date of study initiation: 4-17-1998
GLP compliance: GLP
QA report: Yes
Methods:
Dosing:
Species/strain: Dog/beagle
Drug lot #



Study design: Eight dogs each received 10 dorsal, SC implants (2 each of 4 test materials and 2 USP Reference Standard Negative Control plastic strips), 5 on each side of the midline. The location of each material was randomly rotated among the 8 dogs. After 90 days of implantation, the dogs were euthanized and the local implant sites were evaluated both macroscopically and microscopically to assess local tissue reaction.

Results:

Table 5.**The average severity score of tissue reactions graded as 1-5 for microscopic findings and 0-4 for macroscopic findings**

Tissue reaction	Rate controlling Membrane	Piston	Diffusion moderator	Titanium reservoir	USP negative control plastic
Fibrous encapsulation	1.4	1.3	1.1	1.9	2.1
Infilterate, mixed mononuclear	0.7	0.5	0.2	0.4	0.8
Fibroplasia, active	0.9	0.5	0.9	0.4	0.8
Infiltrate, macrophages	0.3	0.3	0.6	0.0	0.3
Infiltrate,macro phages pigmented	0.7	0.0	0.2	0.0	0.0
Hemorrhage, acute	0.1	0.0	0.0	0.0	0.0

Total macroscopic score (capsule + vascularity + fluid) for the USP Reference Standard Negative Control Plastic and the 4 implant components was 2.1 + 0.3 (mean + SD), which on the 0-12 scale presented mild reaction.

Summary: The macroscopic and microscopic scores indicated that the implanted materials were as biocompatable as the USP negative control material, because reactions of similar severity were seen in the negative control and the test material implantation sites. No evidence of infection was found in any of the sections.

Study title: USP 23: Biological testing of pellets, thermoplastic polyurethane (Tecoflex, HP-60D-20) Code number 0003074, control number 549596.

Study #: TR-96-4904-047.
Volume/page: 1.44/1
Conducting laboratory and location: [redacted]
Date of study initiation: 6-21-1996
GLP compliance: GLP
QA report: Yes
Methods:
Dosing:
Species/strain: mice and rabbits
Sex, age and weight: N/A
Drug lot#: Tecoflex Lot No. E999-03259
Purpose of the test: USP 23 Biological tests are designed to test the suitability of plastic and polymeric materials for use in fabricating containers, for use in parenteral preparations and for use in medical devices, implants and other systems. These tests evaluate the response of animals and living animal tissue following direct contact with pieces of the test material or injection of extracts prepared from this material.
Study design: Biological response of animals to extracts of the test material was determined following single-dose injections of the extracts into mice and intracutaneous injections of the extract into rabbits. Samples of the test article were also evaluated for biological response following implantation of the material into the paravertebral muscle of rabbits for 7 days.
Tecoflex, HP-60D-20 pellets were molded into rods, annealed, irradiated and extracted in 4 different media (0.9% sodium chloride, 5% alcoholic solution in sodium chloride injection, polyethylene glycol 400 and cottonseed oil) for 72 hours at 50 ^{0}C.
In the **systemic toxicity test,** mice were injected with the test extract (5 mice/extract) at a dose of 50 ml/kg for sodium chloride, alcoholic solution and cottonseed oil and 10 g/kg for polyethylene glycol. The sodium chloride and alcoholic solution were injected intravenously while the polyethylene and cottonseed oil preparation by the intraperitonial route. Mice were observed immediately after dosing and at 4, 24, 48 and 72 hours post-dosing.
In the intracutaneous toxicity in rabbits, 2 animals were used per pair of extracts. A 0.2 ml of extract of the test article was injected into 5 separate sites on the right side of the back of each rabbit, and 0.2 ml of control blank on the left side. Observations for erythema and edema were conducted at 24, 48 and 72 hours after injection. Reactions were scored on a 0-4 basis. A difference between test and control blank >1.0 was considered to be unacceptable.
Results: In the systemic injection test none of the animals treated with test material extracted in 4 extraction media showed a greater reaction than observed in the animals treated with the blanks.

In the **intracutaneous injection test,** none of the average scores were significantly higher (>0.5) than the average scores for the corresponding blanks. Microscopic evaluation of the implantation sites classified the material as a slight irritant when compared with the USP negative control implant.

Summary: The test article met the requirements of Class VI-50 ^{0}C plastics.

USP 23: Biological testing of water washed pellets, HDPE (Petrothene, LS6901-00) Code number 0002169, control number 539395 (study No. TR-96-4904-053) and similar testing for water washed pellets, thermoplastic elastomer (C-Flex-LS55A) code number 0002664, control number 540295 (study No. TR-96-4904-054) were conducted as for Tecoflex, HP-60D-20, described above.

Results: Test articles met the requirements for Class VI-50 ^{0}C plastics as described in the USP 23.

Study title: In vitro biological testing of Tecophilic HP-60D-20 (code No. 0003074, control No MV9720451): USP elution and MTT assay.

Study No.: TR-98-5904-016
Volume/page #: 1.44/116
Conducting laboratory and location: [redacted]
Date of study initiation: 8-23-1996
GLP compliance: GLP
QA report: Yes

Methods:

The elution test is a qualitative cytotoxicity test designed to determine the biological reactivity of extracts of elastomeric plastics and other polymeric materials.

In the USP elution test, extracts of the test article and extracts of the positive control (latex) and negative control (USP Reference Standard Negative Control plastic) articles are added to monolayers of L-929 mouse fibroblast cells in 6-well plates. Cells are examined microscopically before treatment and then 24 and 48 hours after treatment. Cytopathic responses are assigned using USP reactivity grades ranging from None to Severe (0-4), representing responses that range from no effect to total cell lysis.

In the MTT assay, non-morphologic criteria are utilized to assess cytotoxicity. It is a spectrophotometric method for determining cell viability in culture. The cytotoxic response in the MTT assay is determined by comparing cell viability in L-929 mouse fibroblast cell cultures incubated with the test article extract or dilutions of the extract to that of cultures treated with the negative control extract.

The mitochondrial dehydrogenase-dependent reduction of the yellow tetrazolium salt, MTT, in viable cells yields a blue formazan product. After solubilization in an adequate solvent, formazan production is quantified using a scanning spectrophotometer ([redacted]) and relative toxicity is expressed as either the test material concentration (IC_{50}) or dilution (ID_{50}) resulting in a 50% decrease in formazan production.

Results: In the elution test, no cytopathic changes were observed except in the positive control latex extract. In the MTT assay, treatment with the test article or dilutions of the extract resulted in mean cell viability ranging from 94-98% relative to negative control cell viability.

Summary: Both in the USP elution test and the MTT assay, Tecoflex HP-60D-20 was considered non-cytotoxic.

Using the USP elution and MTT assay, it was reported that the following implant components were also not cytotoxic and as such considered to be biocompatable:

1. Pellets, Thermoplastic polyurethane (Tecoflex HP-60D-20), Code No. 0003074, Control No. 549596 (study No. TR-96-4904-049)
2. Pellets, HDPE (Petrothene LS6901-00), Code No. 0002169, Control NO. 539395 (study No. TR-96-4904-025)
3. Pellets, Thermoplastic elastomer (C-Flex LS55A), Code NO. 0002664, Control No. 540295 (study No. TR-96-4904-024)
4. C-FLEX LS55A, Code NO. 0002664, Control No. 560296 (study No. TR-96-5904-017)

Genotoxicity testing of DUROS implant components

The polymeric components of DUROS Leuprolide Implant were tested for their potential to cause genotoxicity using the following tests as outlined in the International Conference on Harmonization (ICH) of Technical requirements for Pharmaceuticals for Human use.

Salmonella-Escherichia coli/mammalian-microsome reverse mutation assay
Chromosomal aberrations in Chinese hamster ovary (CHO) cells and
In-vivo mouse micronucleus assay

The following implant components were tested:

Extracts of Tecophilic HP-60D-20 (Code No. 0003074, Control No. MV9720451) polyurethane
Extracts of HDPE (Petrothene LS6901-00) (Code No. 0002169, Control No. 539395)
Extracts of C-Flex LS55A (Code No. 0002664, Control No. 560296)

Extraction method: Extracts of the test article were prepared using the USP guidelines of 3 cm^2 total surface area per ml of extractant in saline or DMSO. For extraction, test article was injection molded into "dog bone" shaped bars under conditions similar to those used for clinical parts fabrication. Bars were washed, dried, annealed, and irradiated. The "dog bones" were extracted in saline (0.9% NaCl) and PEG 400 for polyurethane and in saline and DMSO for the other two at 50 + 1.5 ^0C for 72 + 2 hours. Extracts of molded parts were evaluated for their genotoxic potential in either the presence or absence of mammalian microsomal enzymes. Vehicle extract controls and appropriate positive controls were included in all assays.

Study title: Extracts of Tecophilic HP-60D-20 (Code No. 003074, Control No. MV9720451): Salmonella-Escherichia coli/mammalian microsome reverse mutation assay with a confirmatory assay.

Study No.: TR-98-5904-009
Volume/page: 1.45/1
Conducting laboratory: [redacted]
Date of study initiation/completion: 4-27-1998/9-14-98
GLP compliance: Yes
QA report: Yes
Test article lot No.: As given in study title
Study endpoint: Bacterial mutagenesis

Methodology: In this plate incorporation methodology, the S9 mix (where appropriate), the tester strain, and the test article extracts were combined in molten agar which was overlaid onto a minimal agar plate. Following incubation at 37 + 2 ^0C for 53 + 4 hours, revertant colonies were counted.

Strains/species/cell lines: TA98, TA100, TA1535, TA1537 and Escherichia coli strain $WP2_{uvr}A$.
Basis of dose selection: Cytotoxicity based on bacterial background lawn thinning or disappearance and decrease in the number of revertant colonies/plate or test article extract precipitate. The basis of high dose selection was not provided but it was stated that a minimum of 3 non-toxic dose levels was required to evaluate assay data.
Positive controls: Positive controls for respective tester strains were used and they showed at least 3-fold increase over the mean value of the vehicle (extract) control for the strain.
Criteria for a positive response: For a test article extract to be considered positive, it must produce at least 2 fold increase in the mean revertants/plate of at least one of the tester strains TA98, TA100 and $WP2_{uvr}A$ and at least 3 fold increase for strains TA1535 and TA1537.
Doss used: The doses of the article extract were 20, 50, 100, 150 and 200 ul of extract/plate for both the saline and DMSO extracts. The cultures were dosed first with 200 ul of saline extract, mixed, then followed by the addition of 200 ul of DMSO extract so that the test system was exposed to both extracts and a total volume of 400 ul. After the initial assay, confirmatory assay was performed.
Note: Other 2 components of the DUROS implant ie., extracts of HDPE (Petrothene LS6901-00) and extracts of C-Flex LS55A were tested under study Nos. TR-98-5904-006 and TR-98-5904-003 respectively.
Note: It was reported that DMSO reacted with thermoplastic polyether urethane (polyurethane), and therefore was replaced with PGE 400 as an extraction vehicle.
Results: The test articles did not cause a positive increase in the mean number of revertants per plate with any of the tester strains either in the presence or absence of microsomal enzymes.

Study title: Extracts of Tecophilic HP-60D-20 (Code No. 0003074, Control No. MV9720451): Chromosomal aberrations in Chinese hamster ovary (CHO) cells.

Study No.: TR-98-5904-010
Volume #/page#: 1.46/1
Conducting laboratory: [redacted]
Date of study initiation/completion: 5-14-98/2-26-99
GLP compliance: Yes
QA report: Yes
Test article lot #: as given in study title
Study endpoint: cytogenetic evaluation of chromosomal damage

Methodology: In this assay, test article extracts were prepared as described under the Ames test except that a PEG400 extract of the test article was prepared instead of a DMSO extract. CHO cells were exposed to extracts of the test material in the presence and absence of mammalian microsomal enzymes (S9 mix). At predetermined intervals after exposure, cells were arrested in metaphase with 0.1 ug/ml colcemid. Cells were then harvested, stained, and evaluated microscopically for evidence of chromosomal aberrations in chromosomes or chromotids.
Replicate cultures of CHO cells were incubated for 17.8 hours without metabolic activation or 3 hours with metabolic activation and harvested 20 hours from the initiation of treatment.
Strains/species/cell lines: CHO cells
Doses used: Cultures were dosed sequentially with 10.0, 7.5, 5.0, 2.5 and 1.0 ul/ml of PEG extract and 100, 75, 50, 25, and 10 ul/ml of sterile saline extract, respectively. The vehicle control cultures were dosed with 10 ul/ml of the sham PEG extract and 100 ul/ml of the sham sterile saline extract. A confirmatory assay was performed after the initial trial.
Assay acceptance criteria: The negative and vehicle control culture must contain less than 5% cells with aberrations. Positive control must be significantly higher ($p<0.01$) than the vehicle controls. There should be at least 3 analyzable dose levels. If aberration results are negative and there is no significant

reduction (approx >50%) in mitotic index, the assay must include the highest applicable dose (PEG and sterile saline extracts of 10 and 100 ul/ml, respectively).
Essay evaluation criteria: 1. Percentage of cells with structural aberration
2. Percentage of cells with more than one structural aberration
3. Evidence of a dose-related increase in aberrations
Positive response: A significant increase in the number of cells with chromosomal aberrations is observed at one or more dose levels.
Negative response: no significant increase is observed in the number of cells with chromosomal aberrations for any of the dose levels.

Chromosomal aberrations in Chinese hamster ovary cells was also run for the following 2 DUROS implant components:

Extracts of HDPE (Petrothene LS6901-00) (Code No. 0002169, Control No. 539395). Study No. TR-98-5904-007
Extracts of C-Flex LS55A (Code No. 0002664, Control No. 560296). Study No. TR-98-5904-004

For the above 2 studies extraction was with DMSO rather than with PEG400.

Results: No visual signs of toxicity were reported in any of the test cultures. No reductions were observed in the mitotic indices of the cultures analyzed as compared with the solvent control cultures. Chromosomal aberrations analyzed from cultures treated with 25.0/2.5, 50.0/5.0. 75.0/7.5, and 100.0/10.0 ul/ml of saline/PEG or DMSO test material extracts demonstrated no significant increase in cells with chromosomal aberrations, polyploidy, or endoduplication as compared with solvent control cultures.

Summary: It was concluded that saline and DMSO extracts of DUROS implant components were negative for inducing chromosomal aberrations in CHO cells with and without metabolic activation.

Study title: Extracts of Tecophilic HP-60D-20 (Code No. 0003074, Control No. MV9720451): in vivo mouse micronucleus assay.

Study No.: TR-98-5904-011
Volume#/page #: 1.47/1
Conducting laboratory: [redacted]
Date of study initiation/completion: 4-27-1998/11-10-1998
GLP compliance: Yes
QA report: Yes
Test article lot #: MV9720451
Study endpoint: micronucleated polychromatic erythrocytes
Methodology: Extracts of molded parts were evaluated for their in vivo clastogencic (chromosome breaking) activity and/or their ability to induce disruption of the mitotic apparatus by detecting micronuclei in polychromatic erythrocytes in the mouse bone marrow.
A single dose of the material extract or control article was administered by intravenous injection (saline) or intraperitoneal injection (sesame oil) to groups of CD-1 mice. Hind limb bones were extracted from euthanized mice either 24 or 48 hours later. The bone marrow from each mouse was flushed, centrifuged, smeared on slides, and stained. Enucleated immature RBC's [polychromatic erythrocytes (PCE)] were examined microscopically for the presence of micronuclei. Assay design was based on OECD Guidelines 474, 12/96 final draft. Extracts were prepared as described under Ames test.
Strain/species/cell lines: Crl:CD-1BR strain/mouse

Study design: was as follows:

Group #	Treatment	Acute treatment sampling time 24 hours	48 hours
1	Positive control	5	-
2	Vehicle control (saline)	5	5
3	Test article extract (saline)	5	5
4	Vehicle control (seasame oil)	5	5
5	Test article extract (seasame oil)	5	5

The dosing volume was 50 ml/kg. High dose was with undiluted extract.

Study acceptance criteria: vehicle control usually should be less than 0.4% micronucleated PCE's. Positive control response must be statistically significantly higher than the vehicle control group and be consistent with historical control data. High dose should be the neat (undiluted) extract. High dose should allow animal recovery and survival.

Criteria for positive clastogenic response: the detection of a statistically significant percentage of micronucleated PCE's above the sesame oil and saline control values for at least one dose level and a statistically significant dose-related response.

Results:

There were signs of clinical toxicity in animals treated with the saline or sesame oil control and saline and sesame oil extracts of the test articles.

As shown in table below, Tecophilic HP-60D-20 extracts were neither cytotoxic to the bone marrow (PCE:NCE ratio), nor they increased percentage of micronucleated PCE's.

Table 6. **Effect of Tecophilic HP-60D-20 in mouse micronucleus assay**

Treatment	Dose	Harvest time(h)	% micronucleated PCE's mean+SE of 2000/animal	Ratio PCE:NCE mean +SE
Controls				
Vehicle				
Saline		24	0.04+0.02	0.25+0.05
		48	0.05+0.02	0.31+0.04
Sesame oil		24	0.03+0.01	0.43+0.03
		48	0.02+0.01	0.26+0.04
Positive	80 mg/kg	24	3.46+0.33**	0.45+0.01
Test article				
Extract				
Saline		24	0.01+0.01	0.33+0.03
		48	0.05+0.02	0.39+0.04
Sesame oil		24	0.02+0.004	0.34+0.013
		48	0.05+0.00	0.36+0.04
Historical control data				
Vehicle controls			0.069+0.004	0.599+0.013
Positive CP controls			3.061+0.099**	0.615+0.024

** Significantly different compared with vehicle controls. Positive control CP=cyclophosphamide

Findings for the other 2 implant components i.e. Petrothene LS6901-00 and C-Flex LS55A tested under studies #s TR-98-5904-008 and TR-98-5904-005 respectively were similar.

Summary: The saline and sesame oil extracts of all components of the DUROS implant were considered negative in the mouse bone marrow micronucleus test under the conditions of exposure in this assay.

Sponsor has also included results of the studies conducted in 1983 on Biocompatibility and safety evaluation of Tecoflex EG-60D and Tecoflex 80A. These studies were sponsored by Thermo Electron Corporation, Waltham, MA and were conducted by Bioassay Systems Corporation as projects numbers 11308 and 11945, respectively.
Both Tecoflex polyurethanes gave negative results in the following tests:

Systemic injection and intracutaneous tests:
In the systemic injection test in mice, test and control samples were injected i.v. when extracted in 0.9% saline and alcoholic sodium chloride and i.p. when extracted in PGE400 and cottonseed oil. The sample was extracted at a ratio of 6 cm^2/ml of extractant at 50 ^{0}C for 72 hours. The dose was 50 ml/kg except for 10g/kg for PGE400. Mice were examined at 2, 24, 48 and 72 hours for physical signs of toxicity, aberrant behavior and deaths.

In the intracutaneous test in rabbits, 0.20 ml of the test sample was injected at 10 sites on one side and blanks on the contralateral side. Sites were examined at 24, 48 and 72 hours post-injection and scored for erythema and edema according to Draize scoring system. Sample was considered non toxic if difference between the test and control did not exceed 1.0.

Intramuscular implantation in rabbits: Solid strips of Tecoflex and USP negative reference plastic was implanted directly into the paravertebral muscle. Rabbits were sacrificed after 7 and 21 days for macroscopic and microscopic examination of the implant sites.

Agar overlay cytotoxicity test using L929: Test and control samples were placed directly on the agar surface. Each plate contained 2 test samples and a positive and a negative control. Plates were incubated for 24 hours and then examined microscopically for zones of decolorization and cell lysis. The degree of cytotoxicity was scored according to decolorization/lysis ratio. Only samples producing lysis scores of 1 or greater at any of test sites were considered cytotoxic.

Direct exposure cytotoxicity test: was conducted using confluent human diploid fibroblasts maintained in monolayer culture. Cell were incubated for 24 hours and then scored for cell lysis or vacuolization. Scores of 1 or greater were considered being cytotoxic.

Red blood cell hemolysis (direct contact): Freshly diluted, anticoagulated human blood was added to tubes containing 0.9% sodium chloride (negative control) or test sample in 0.9% sodium chloride or deionized water as positive control. After incubation for 60 minutes at 37 ^{0}C, tubes were centrifuged. The amount of hemoglobin released in the medium by RBCs was measured spectrophotometrically at 545 nm. A sample producing percentage hemolysis score of greater than10% was considered toxic.

Ames/Salmonella mutagenicity test: Aliquots of saline extracted test sample (10, 30, 100, 300, or 1000 ul) or controls (100 or 1000 ul) were used. Samples were tested in duplicates in Salmonella strains TA98, TA100, TA1535, TA1537 and TA1538, both in the presence and absence of rat liver metabolic activation system. A test sample was considered mutagenic if it induced a concentration-dependent response in which the number of revertants per plate exceeded 2 times the negative control mutation rate.

Results: Both Tecoflex EG-60D and Tecoflex 80A were negative in all of the above described tests.

Sponsor has also provided a list of FDA-approved medical devices currently using Tecoflex polyurethanes. These include catheters, surgical stents, fiber optic imaging, blood bags, canulas and naso-gastric tubes.

In addition the sponsor has provided an extensive nonclinical bibliography and references along with reprints of publications for the following components:

Titanium, polyurethane, high density polyethylene, thermoplastic elastomer (C-flex), silicon medical fluid, dimethyl sulfoxide, sodium chloride, magnesium stearate, polyvinylpyrrolidone (PVP), disodium carboxymethylcellulose and PEG-400.

Overall summary:

Leuprolide acetate, the drug substance being reviewed under this NDA is indicated for the treatment of advanced prostate cancer.
Leuprolide acetate is a synthetic nonapeptide of the naturally occurring gonadotropin-releasing hormone (Gn-RH of LH-RH). It is a Gn-RH agonist and possesses 80-100 times greater potency than the native GnRH.
Leuprolide acetate acts as a potent inhibitor of gonadotropin secretion when given continuously and in therapeutic doses resulting in suppression of ovarian and testicular steroidogenesis after an initial stimulation.
Leuprolide acetate is not active when given orally.
Daily injection and depot formulations of leuprolide acetate have been used in sex hormone ablation therapy since the introduction of this active substance to the market in the United States in 1985.
Leuprolide acetate as Lupron (TAP Holdings Inc) for injection and for depot suspension are FDA approved products under NDAs 19-010, 19-732, 19-943, 20-011, 20-263, 20-517 and 20-708 for many indications such as palliative treatment of prostate cancer, endometriosis, treatment of uterine fibroids, and precocious puberty.
At present leuprolide acetate as Lupron for the palliative treatment of prostate cancer is available either as one month or 4-month formulations and to maintain continuous therapeutic effectiveness these need to be administered every month or every 4 months, respectively.

DUROS Leuprolide Implant (Viadur), the formulation under consideration, is designed to be administered once a year.

Viadur is a nondegradeable, osmotically driven miniaturized implant designed to deliver leuprolide acetate continuously at a nominal rate of 120 ug/day over a period of one year.

The pharmacology, pharmacokinetics and toxicology of leuprolide acetate have been extensively studied in preclinical studies. Its safety and efficacy also have been well established in the clinical studies.

Viadur has been tested in long term studies in rats, dogs and swine for its local reaction. These studies demonstrated that the implant caused only mild to moderate local reaction and was deemed biocompatable. All components of Viadur were negative in a battery of genotoxicity tests.

Results of sponsor's conducted studies along with review of the submitted published literature provided good evidence for the safety of the proposed leuprolide formulation for the palliative treatment of advanced prostate cancer.

Conclusion: Pharmacology considers that the DUROS Implant is safe for it intended indication for the palliative treatment of advanced prostate cancer.

Communication Review:

Labeling review: Labeling is essentially similar to current Lupron-3 month and Lupron-4 month labels, which have been previously approved by the FDA under various NDAs for many therapeutic indications. The only recommended change to be made in labeling is to express doses used in the carcinogencity studies as multiples of the human therapeutic dose on either systemic drug exposure or on body surface area basis.

Recommendations:

Internal comments: Based on the fact that leuprolide acetate is a FDA approved drug substance under various NDAs for both hormone-dependent malignancies (prostate cancer), benign uterine disorders (endometriosis, uterine fibroids and leiomyoma) and for precocious puberty, along with extensive safety data developed by the sponsor for the DUROS components, Pharmacology recommends approval of NDA 21-088 for the palliative treatment of advanced prostate cancer.
External recommendations (to sponsor): as indicated in draft letter
Draft letter content for sponsor: "Please express doses used in the carcinogencity studies as multiples of the human therapeutic dose on either systemic drug exposure or on body surface area basis.

Reviewer signature/team leader signature: /S/ /S/
Draft date(# of drafts)
Memorandum of Non-concurrence (if appropriate, attached):
Addendum to review (if necessary):
Appendix/attachments: Copies of IND52,635 reviews. Submission dated 2-7-1997 & 7-8-1997.