

## Drug Class Review: Luteinizing Hormone Releasing-Hormone (LHRH) Agonists in Prostate Cancer

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### OBJECTIVE

- To review the efficacy, safety, and administration of the LHRH agonists currently available in 1, 3, 4, or 12-month preparations for the treatment of prostate cancer:

#### Currently available products

Generic Name	Goserelin	Leuprolide	Leuprolide	Leuprolide	Triptorelin
Brand Name	Zoladex®	Lupron Depot®	Viadur®	Eligard™	Trelstar Depot™ and LA™
Manufacturer	AstraZeneca Pharmaceuticals	TAP Pharmaceuticals	Bayer	Atrix Laboratories, Inc.	Pharmacia Oncology

- To define selection criteria in the contracting of agents for the Veterans Health Administration.

### I. PHARMACOLOGY<sup>1-4</sup>

LHRH agonist analogues suppress endogenous testicular gonadotropin synthesis, causing a hypogonadal condition. Chronic administration of LHRH agonists exerts constant stimulation on the pituitary gland, causing desensitization and down-regulation of pituitary LHRH receptors leading to suppression of LH and FSH levels. In men, testosterone levels diminish to castrate levels within 14-28 days of therapy, and reverse upon discontinuation. A transient stimulatory phase of 1-2 weeks occurs due to elevated testosterone and dihydrotestosterone levels. At this point in therapy, 4-63% (mean 11%) of patients experience a “flaring” of disease symptoms (see safety).

### II. INDICATIONS<sup>5</sup>

The following dosage forms have received FDA approval for prostate cancer indications. For a complete listing of other indications, refer to LHRH Agonist Use in Gynecologic Disorders at [www.vapbm.org](http://www.vapbm.org).

	Goserelin 3.6 mg 1 month depot	Goserelin 10.8 mg 3 month depot	Leuprolide 7.5 mg 1 month depot	Leuprolide 22.5 mg 3 month depot	Leuprolide 30 mg 4 month depot	Leuprolide 65 mg 12 month implant	Leuprolide 7.5mg in Atrigel 1 month depot	Triptorelin 3.75mg 1 month depot	Triptorelin 11.25mg 3 month depot
<b>Palliative treatment of advanced prostate cancer</b>	X	X	X	X	X	X	X	X	X
<b>In combination with flutamide for the management of locally confined prostate cancer, 8 weeks prior and during radiation therapy</b>	X	X							

**III. PHARMACOKINETICS**<sup>5-10</sup>**TABLE 1.**

	<b>Goserelin</b>	<b>Leuprolide Depot</b>	<b>Leuprolide Implant</b>	<b>Leuprolide Atrigel</b>	<b>Triptorelin</b>
Time to Peak Plasma Concentration	12-15 days (3.6mg) 1.8 hours (10.8mg)	4 hours	4 hours	5 hours	1 hour (3.75mg) 2.9 hours (11.25mg)
Onset of Steady State Levels	9 days (3.6mg) 4 days (10.8mg)	21 days	3 days	2 days	
T <sub>1/2</sub>	4.2 hours	3-4 hours	3-4 hours	3 hours	2.8 hours (normal)
V <sub>d</sub>	44.1L	27L	27L	27L	30-33L
Protein Binding	27.3	43-49%	43-49%	43-49%	No evidence
Metabolism	By hydrolysis	To smaller, inactive peptides	To smaller, inactive peptides	To smaller, inactive peptides	Unknown
Excretion	Via hepatic metabolism and urinary excretion	<5% recovered in urine	<5% recovered in urine	<5% recovered in urine	Liver and kidney
Hepatic/Renal Impairment	Cl <sub>CR</sub> <20ml/min → ↑t <sub>1/2</sub> ↓clearance but No change in dosing Hepatic: no change	Not determined	Not determined	Not determined	t <sub>1/2</sub> =7.7 hours (renal impairment) 7.6hours (hepatic impairment)

Despite a slow absorption rate in the initial 8 days of therapy, goserelin administration every 28 days provides suppression of testosterone levels equivalent to surgically castrated men. Measurable serum concentrations of the drug persists throughout the 28-day dosing period with administration of the 3.6 mg monthly depot formulation, and appears similar with the 10.8 mg per 3 month depot formulation. Elimination of goserelin occurs through hepatic metabolism and urinary excretion. Although a decreased creatinine clearance (<20 ml/min) did not alter adverse effects, the serum elimination half-life increased from 4.2 hours in patients with normal renal function to 12.1 hours in patients with impaired renal function.

Leuprolide monthly and 3-month formulations release the drug at a constant rate after onset of steady state levels during the third week of dosing. The 4-month formulation of leuprolide reaches steady state levels during the fourth week after dosing and continues its release at a constant rate thereafter. The 12-month formulation of leuprolide maintains steady-state concentrations from day 3 through the remainder of the 12-month treatment period. Leuprolide in Atrigel achieves steady state levels after day 2. Animal studies in rats and dogs have shown leuprolide to undergo metabolism to smaller, inactive peptides (a pentapeptide – Metabolite I; tripeptides – metabolites II and III; and a dipeptide – Metabolite IV). Less than 5% of a single dose is recovered as parent or major metabolite (M-I) in the urine. The pharmacokinetic parameters of leuprolide in hepatically and renally impaired patients have not been determined for the intramuscular injection, implant, or formulation in Atrigel.

Limited pharmacokinetic data exists on the depot formulation of triptorelin. One dose of Trelstar Depot 3.75mg or Trelstar LA 11.25mg administered intramuscularly to healthy male volunteers attained a mean C<sub>max</sub> of approximately 28.43 ng/ml at a median T<sub>max</sub> of one hour and 38.5 ng/ml at 2.9 hours, respectively. Both the monthly and 3-month formulations provide plasma concentrations of triptorelin over the dosing periods of 1 month and 3 months, respectively. Elimination occurs through both renal and nonrenal (hepatic) routes and elimination is altered with renal and/or hepatic impairment. Metabolism of triptorelin in humans remains unknown.

**IV. SAFETY**<sup>5-10</sup>

Adverse effects of the LHRH agonists occur corollary to the expected physiological effects of decreased testosterone levels induced by these agents. The initial disease flare during the first 1-2 weeks can worsen preexisting disease conditions such as bone pain, spinal cord compression, and hydronephrosis. These agents can also cause hot flashes, impotence and reduced libido. Additional adverse events appear in Table 2.

**TABLE 2.** Adverse Reactions Occurring at a >5% Frequency for Subjects Administered Goserelin 3 - Month, Leuprolide 3-Month, Leuprolide 12-Month, Leuprolide in Atrigel, and Triptorelin 3-month Formulations

Adverse Reactions ( $\geq 5\%$ )	Goserelin depot (3 month) n=157	Leuprolide depot (3 month) n=94	Leuprolide implant (12 month) n=131 (Insufficient information)	Leuprolide Acetate in Atrigel for SC n = 128 (Insufficient information)	Triptorelin Pamoate LA (3 month) N = 174 (Insufficient information)
	% All	% All	% All	% All	% All
<i>Central/Peripheral Nervous System</i>					
Dizziness/Vertigo	-	6.4	-	-	-
Insomnia/Sleep disorders	-	8.5	-	-	-
Neuromuscular disorders	-	9.6	-	-	-
Pain	14	26.6	-	-	-
Depression	-	-	5.3	-	-
<i>Endocrine</i>					
Gynecomastia/breast tenderness/changes	8	-	6.9	-	-
Hot flashes	64	58.5	67.9	56.7	73
<i>Musculoskeletal</i>					
Bone pain	6	-	-	-	-
Skeletal pain	-	-	-	-	13.2
Joint disorders	-	11.7	-	-	-
<i>Digestive System</i>					
GI Disorders	-	16	-	-	-
<i>Respiratory System</i>					
Respiratory Disorders	-	6.4	-	-	-
<i>Skin and Appendages</i>					
Skin reaction	-	8.5	-	-	-
Sweating	-	-	5.3	-	-
Edema in legs	-	-	-	-	6.3
Leg pain	-	-	-	-	5.2
<i>Urogenital System</i>					
Testicular Atrophy	-	20.2	-	5	-
Urinary Disorders	-	14.9	7.6	-	-
<i>Miscellaneous</i>					
Asthenia	5	7.4	7.6	-	-
Headache	-	6.4	-	-	6.9
Malaise and Fatigue	-	-	-	17.5	-
Injection Site Reaction	-	13.8	-	34.6	-

Adapted from:

Package Insert. Lupron (Leuprolide). Deerfield, IL: TAP Pharmaceuticals, March 2000.

Package Insert. Zoladex (Goserelin). Wilmington, DE: Zeneca Pharmaceuticals, February 1999.

Package Insert. Viadur (Leuprolide Acetate Implant). West Haven, CT: Bayer Corporation Pharmaceutical Division, October 2000.

Package Insert. Eligard (Leuprolide acetate in Atrigel). Fort Collins, CO. Atrix Laboratories, Inc. January 2002.

Package Insert. Trelstar LA 11.25mg (Triptorelin Pamoate). Kalamazoo, MI: Pharmacia & Upjohn Company, August 2001.

V. DOSAGE AND ADMINISTRATION<sup>5-10</sup>

TABLE 3.

Drug	Preparation and Administration
Goserelin 3.6mg SC every 28 days Goserelin 10.8mg SC every 3 months	<ul style="list-style-type: none"> <li>Administer into upper abdomen</li> <li>Needle is tunneled parallel to the skin and fat</li> <li>When the hub touches the skin, the needle is pulled back 1 cm to insert the pellet</li> <li>3.6mg dose has 16g needle</li> <li>10.8mg dose has 14g needle</li> </ul>
Leuprolide Depot 7.5mg IM every 28 days Leuprolide Depot 22.5mg IM every 3 months Leuprolide Depot 30mg IM every 4 months	<ul style="list-style-type: none"> <li>Provided in a prefilled dual chamber syringe</li> <li>Syringe is activated by the plunger, mixing the diluent with the lyophilized microspheres and forming a suspension</li> <li>All syringes have a 23g 1.5inch needle</li> <li>Volume after reconstitution: 7.5mg-1.1ml, 22.5mg and 30mg-1.7ml</li> </ul>
Leuprolide Implant 65mg every 12 months	<ul style="list-style-type: none"> <li>In-office physician procedure</li> <li>Identification of the insertion site</li> <li>Preparation of the sterile field</li> <li>Anesthetize the site</li> <li>Make incision and insert the implant; close with steri-strips</li> <li>Implant must be surgically removed after 12 months</li> <li>A kit is provided containing all materials for insertion &amp; removal</li> </ul>
Leuprolide acetate in Atrigel 7.5mg SC every 28 days	<ul style="list-style-type: none"> <li>Provided in 2 syringes: one with the polymer/solvent and one with Leuprolide powder</li> <li>Allow to come to room temperature (must be stored refrigerated)</li> <li>Change plunger in Leuprolide syringe, unscrew caps on both syringes, connect and mix thoroughly by pushing contents back and forth between syringes for 45 seconds</li> <li>Disconnect the syringes, attach 20g ½inch needle (provided)</li> <li>Must be used within 30 minutes</li> </ul>
Triptorelin	<ul style="list-style-type: none"> <li>Add 2 ml sterile water for injection, USP (no other diluent should be used)</li> <li>Shake well to disperse particles and form a uniform suspension (milky)</li> <li>Withdraw entire contents and administer immediately using a 20g needle</li> <li>If not used immediately, discard</li> </ul>

Goserelin 3.6 mg depot is a pellet administered into the abdominal fat with a 16-gauge needle. The 10.8 mg 3-month depot formulation is administered with a 14-gauge needle.

Leuprolide depot is available in a prefilled dual-chamber syringe containing sterile, lyophilized microspheres, which, when combined with diluent, becomes a suspension for intramuscular injection. All of the adult formulations (1-month, 3-month, and 4-month) are supplied with the same syringe system, which is comprised of a 23 gauge (22 gauge interbore) 1.5-inch needle. The actual volume of drug after reconstitution is 1.1 ml for Leuprolide 7.5 mg and 1.7 ml for both Leuprolide 22.5 mg and Leuprolide 30.0mg. The leuprolide implant delivery system depends on osmosis to release leuprolide acetate at a constant rate for 12 months. A physician inserts the implant in an in-office procedure. The leuprolide in Atrigel comes in 2 syringes, which are connected for mixing purposes.

The Trelstar Depot and Trelstar LA Debioclip single-dose delivery system consists of a vial with a flip-off seal containing sterile, lyophilized triptorelin pamoate microgranules equivalent to 3.75mg and 11.25mg of triptorelin peptide base, respectively, and a prefilled syringe containing 2 mL sterile water for injection, USP. The Debioclip is attached to the vial, and the needle of the Debioclip will pierce the vial stopper. The 2mL of Sterile Water for Injection is released into the vial and mixed with the powder until a homogeneous suspension is formed. The entire suspension is then withdrawn into the syringe. If the Debioclip syringe system is not used, the lyophilized microgranules contained in the vial need to be reconstituted with 2 ml of sterile water for injection using a syringe fitted with a 20-gauge needle.

Data is lacking from properly designed trials to compare the routes of administration and their effect on patient compliance and adverse effects.

## VI. CLINICAL TRIALS<sup>11-25</sup>

The gold standard in hormonal manipulation to suppress plasma testosterone levels in advanced prostate cancer is orchiectomy. Estrogen, primarily DES, has also been shown to effectively suppress testosterone to castrate levels. Several large studies, including the Veterans Administration Cooperative Urology Research Group (VACURG), compared DES to orchiectomy and found them to be equivalent. A meta-analysis of these studies established that DES is equivalent to orchiectomy; thus orchiectomy or DES should be used as comparators when designing trials of newer agents in advanced disease.

Treatment goals in advanced disease should include: sustained suppression of testosterone to castrate levels, palliation of symptoms, prevention or delay of disease progression, prevention or delay of symptoms, decrease in PSA or prostatic acid phosphatase to normal levels, increase in overall survival, minimal adverse effects, and patient satisfaction as compared to orchiectomy or DES. A summary of trial information is found in **Tables 5-10**.

**Goserelin vs. DES or Orchiectomy.** Goserelin monthly injections were compared in randomized trials to DES or Orchiectomy in advanced prostate cancer. Objective responses, time to progression, and overall survival were similar between the groups. Goserelin caused a flare in disease symptoms within the first two weeks. Serious adverse effects were more common with DES and caused withdrawal from the study in up to 21% of those randomized to this arm.

**Leuprolide vs. DES.** Leuprolide daily and depot were compared in randomized trials to DES. Objective responses, time to progression, and overall survival were similar between the groups. Leuprolide caused a flare in disease symptoms in the first two weeks. Serious adverse effects were more common with DES.

**Triptorelin and Leuprolide in Atrigel.** Phase II studies with these agents have not been published. Comparative data with orchiectomy or DES is not available. Comparative data with triptorelin pamoate 3.75mg and leuprolide acetate 7.5mg depot exists as unpublished data and concludes that triptorelin pamoate and leuprolide acetate are equally effective in achieving and maintaining castration.

**Leuprolide Implant.** Open-label, multicenter trials report that the leuprolide implant delivered leuprolide at a controlled rate for 12 months, providing therapeutic suppression of testosterone in patients with advanced prostate cancer, which may make this formulation an effective alternative to depot injection. QoL data states that >90% of pts were extremely satisfied or satisfied with the overall treatment. However, no QoL comparisons exist between patient experiences with the implant versus patient experiences with LHRH injections.

## VII. SUMMARY OF EFFICACY

There are currently 5 LHRH products approved for use in the palliative treatment of advanced prostate cancer. Two of the new products (Viadur and Eligard) are new formulations of leuprolide. Triptorelin pamoate (Trelstar) is a newer salt of triptorelin; the acetate salt has been used in Europe for several years. A literature search to find published trials comparing LHRH agonists to the gold standard (i.e. orchiectomy or DES) reveals that there are published comparative studies for leuprolide depot and goserelin. The published data on the leuprolide implant is not comparative, has follow-up for only 14 months, and does not include objective response data or survival data. Triptorelin and leuprolide in Atrigel do not have any published data; the data that is available is not comparative, does not include objective response data or survival data, and data is only available in abstract or poster presentation form.

When evaluating efficacy, it is important to assess the majority of the goals of treatment (listed above). LHRH agonists should show equal efficacy (i.e. objective response, palliation of symptoms, delay in progression, decrease in PSA or prostatic acid phosphatase, equivalent overall median survival, minimal adverse effects, improved quality of life) when compared to either orchiectomy or DES therapy in randomized trials with full results published in peer-reviewed journals. There are no published randomized head to head trials between the LHRH agonists.

A summary of published information measuring the efficacy of LHRH agonists compared to orchiectomy or DES:

**Testosterone levels:** All LHRH agonists suppress testosterone to castrate levels by week 3 or 4 and maintain those levels throughout the dosing interval (note: there was a 13% breakthrough rate of testosterone levels above castrate in the triptorelin LA studies. A breakthrough rate of 5% is also reported with leuprolide and goserelin in a small series.<sup>26</sup> The clinical significance is unknown).

**Adverse effects:** The side effect profile is similar in all agents owing to the same mechanism of action. Differences in injection site reactions are minimal, except for the implant, which may have prolonged, though mild, pain at the insertion site.

**Objective response:** Objective responses, based on national criteria (American or British) have been measured and reported with the daily leuprolide, the leuprolide depot, and goserelin.

**Palliation of symptoms:** Assessment of subjective symptom improvement has been reported with leuprolide (daily and depot), goserelin, and triptorelin.

**Decreased PSA/prostatic acid phosphatase:** Decreases reported with all formulations.

**Delay in progression:** Measured and reported for leuprolide (daily and depot), goserelin, triptorelin acetate (not the pamoate approved in the US).

**Equivalent overall survival:** Measured and reported for leuprolide (daily and depot), goserelin, and triptorelin acetate (not pamoate)

**Quality of Life:** No difference reported with triptorelin pamoate versus leuprolide acetate.

Greater than 90% reported extreme satisfaction or satisfaction with leuprolide implant. No comparison reporting difference in QoL between patient experiences with implant versus patient experiences with LHRH injections.

N.B. QoL was also evaluated retrospectively thru the Prostate Cancer Outcomes Data on 431 men who underwent either orchiectomy or therapy with a LHRH agonist (either leuprolide or goserelin). Sexual function was similar in each group before and after therapy. LHRH agonists produced more breast swelling. Patients receiving LHRH agonists reported more worry and overall discomfort and poorer perception of overall health.<sup>27</sup>

**Further Analysis.** A meta-analysis was conducted in 1999 to assess the relative effectiveness and costs of various forms of androgen suppression in advanced prostate cancer. One of the areas studied was the use of monotherapy, including LHRH agonists or antiandrogens. In the analysis, orchiectomy and DES were found to be equivalent in outcomes and used as comparators. When compared in randomized controlled trials, the LHRH agonists studied (leuprolide, goserelin, and busserelin) did not differ statistically from orchiectomy or DES with respect to survival and time to disease progression. When the LHRH agonists were compared to each other, there was no significant difference in survival or side effects between the agents. In the one head to head trial comparing leuprolide and goserelin in combined androgen blockade, the incidence of local injection site reactions was infrequent and occurred at the same rate with leuprolide and goserelin.<sup>28</sup>

## VIII. Utilization and Cost Data

Purchase data prior to this original contract awarded in 1996 showed 46,192 total units of leuprolide acquired by the VA at a cost of \$11,905,799 to the VA system during FY 1995, while 26,479 total units of goserelin purchased during the same time frame cost the VA \$ 5,233,916. After establishment of the contract, goserelin usage slowly increased over the years to 86,023 total units purchased in FY 01, costing the VA system \$34,029,615. Leuprolide utilization decreased to 736 units purchase at a cost of \$476,390 in FY 01. As use of these agents persisted, no significant problems have been reported with respect to the injection/administration of either agent in our system.

**TABLE 4. VA Cost Per Month for LHRH Agonist Agents**

<b>Drug Product</b>	<b>VA Cost per month (\$)</b>
Goserelin 3.6mg (1-month)	140.67
Goserelin 10.8mg (3-month)	134.85
Leuprolide Depot 7.5mg (1-month)	227.21
Leuprolide Depot 22.5mg (3-month)	227.21
Leuprolide Depot 30mg (4-month)	140.00
Leuprolide Implant 65mg (12 month)	144.09
Triptorelin Depot 3.75mg (1-month)	261.74
Triptorelin LA 11.25mg (3-month)	261.74
Leuprolide In Atrigel 7.5mg (1-month)	Not marketed yet

## IX. CRITERIA FOR SELECTION OF FORMULARY AGENTS

Objective response per national guidelines in comparison to orchiectomy or DES

Time to progression and overall survival data in comparison to orchiectomy or DES

Adverse effect profile

Assessment of subjective symptom improvement

Suppression of testosterone to castrate levels over the entire dosing interval

Availability of a 1-month and long duration product is preferred.

Prior to the existing contract, the PBM conducted a survey of practitioners due to the lack of trials comparing the administration of leuprolide depot and goserelin. This survey incorporated the opinions of oncologists and urologists across the VA and focused on the differences in administration between the 2 agents available at that time as they relate to patient treatment. Nineteen of the 22 Veterans Integrated Service Networks responded to the survey. The majority of the oncologists and urologists surveyed expressed that injection site adverse events were not well supported. The results revealed a need to properly train staff and educate patients on the administration of the agents. Also, a small percentage of patients may not have tolerated one agent based on complicating medical or psychosocial factors, and may have required the other product as an alternate.

## **X. RECOMMENDATIONS**

Utilization data to date demonstrates that the VA requires only one agent from this class to treat VA patients with prostate cancer. The preferred agent should treat a majority of patients with the indicated condition. All of the LHRH agonists have indications for the treatment of advanced prostate cancer. Only leuprolide depot and goserelin have sufficient comparative data from randomized trials at this time. The company awarded the contract should offer VA staff (or contracted home healthcare agencies) training on injection/implantation technique and provide an implementation schedule for completion. Availability of this training should persist for the duration of the contract. Also, the manufacturer/distributor of the awarded agent should prepare and supply the VA with VHA approved patient information leaflets.

It is preferred that the agent chosen is available in a 1-month formulation and a long duration formulation. A 1-month formulation is used when starting therapy to assess tolerability. If a patient can't tolerate the particular 1-month LHRH agonist, there is reduced wastage of drug. Theoretically, it should be feasible to start a patient on a 1-month formulation of one LHRH agonist and continue therapy with a longer duration formulation of a different agonist. There is no data supporting or refuting this theory.

The 12-month implant is attractive because of its decreased need for clinic visits. The cost of a clinic visit for an injection has not been quantified. However, it is unlikely that advanced prostate cancer patients won't see their urologist for 12 months at a time. There is also concern about wastage of drug (thus increased costs) if a patient stops responding or expires and the need for a physician to perform the insertion. For comparisons sake, the median survival of a patient with advanced prostate cancer is now greater than 20 months, depending on performance status. This product would be useful in patients who have limited accessibility to medical care.

Since the data comparing leuprolide depot and goserelin show equal efficacy compared to orchiectomy or DES, equivalent survival data, and similar side effect profiles the choice of one of these agents for the VA National Formulary should be based on cost. The 12-month implant should be available as a non-formulary item for those situations where use is warranted.

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**Table 5.** Review of Clinical Trials - **Goserelin vs. DES**

TRIAL	DESIGN	INCLUSION	DOSE/THERAPY	OUTCOMES	RESULTS
Citrin et al. 1991 N=67	OPEN PROSPECTIVE RANDOMIZED MULTI- CENTERED	Histologically confirmed adenocarcinoma of the prostate; Jewett Stage D2 disease with estrogen therapy indicated as primary treatment; Measurable or evaluable disease; Life expectancy of > 3 months; Recovery from definitive local tumor complications; Without evidence of significant infection or effects of major surgery; Written informed consent given voluntarily; Refusal to undergo orchiectomy	Zoladex 3.6 mg sc Q 28 D N=48  DES 3 mg po QD N=19  Pts treated until withdrawal due to a severe adverse drug reaction, disease progression, and unwillingness to continue, or at the discretion of the investigator.  F/U up to 120 weeks	Endocrine effects Efficacy Safety Main end-points: Objective response Time to treatment failure Survival	Median serum T were dec to castrate levels by week 4 with no statistically significant difference between groups  Objective response p = 0.8 Zoladex – 88% DES – 84%  Time to treatment failure not significantly different (p=0.3)  Survival not significantly different bt. groups (p=0.6)  Safety: Zoladex – Hot Flashes 53% DES – Breast Changes 56% Edema 44%
West Midlands Urological Research Study Group N = 250	PHASE III OPEN RANDOMIZED	Histological or cytological diagnosis of prostate cancer; Locally advanced disease (T3/4) or distant metastases; No previous sex hormone or antihormone therapy; No prior orchiectomy; No C/I to estrogen therapy; No incipient spinal cord compression; No previous or concurrent malignancy	Zoladex 3.6 mg sc Q 4 weeks N=124  DES 3mg po QD N=126  Median follow-up time = 19.5 months	Efficacy Objective disease response Time to progression Time to death Tolerance (side effects)  Subjective	Subjective response - no significant difference (p=0.23 with 95% CI $\pm$ 6.7% for both groups) Zoladex 55% DES 45%  Median time to best response: Zoladex - 3 months DES – 9 months  Median time to first response: Zoladex - 3 months DES – 6 months  Survival – no significant difference bt. groups  Safety: Zoladex – Inc. bone pain (5 pts) DES – CV side effects (7 pts)

**Table 6.** Review of Clinical Trials - **Goserelin vs. Orchiectomy**

TRIAL	DESIGN	INCLUSION	DOSE/THERAPY	OUTCOMES	RESULTS
Turkes et al. 1987 N = 359	OPEN RANDOMIZED PHASE III	Histologically confirmed cancer of the prostate; Radiological and/or isotopic evidence of bone metastases; Life expectancy of at least 3 months; Suitable for orchiectomy	Zoladex 3.6 mg sc Q 28 D N=128  Total or subcapsular orchiectomy N=112	Subjective response Urine Flow Activity Score Bone Pain Use of analgesics  Objective response -T- category of the primary tumor; -Prostatic dimension by digital exam (wxl) and/or prostatic volume assessed by rectal ultrasound; -Whole body isotope bone scan and/or x-rays -Other clinically measurable metastases; -Serum total and prostatic acid phosphatase in samples taken prior to rectal examination  Endpoints -Progression of disease -Death -Inability or unwillingness to continue to medication	Subjective response Zoladex 72% Orchiectomy 80%  Serum T below castrate level (<2 nmol/L) for Zoladex group as well as orchiectomy group for up to 48 weeks  Tolerated well with minimal side effects
Kaisary et al. 1988 N = 359	MULTICENTER PROSPECTIVE RANDOMIZED	Histologically confirmed cancer of the prostate; Radiological and/or isotopic evidence of bone metastases and or evidence of soft tissue metastases; Life expectancy of at least 3 months; Fitness to undergo orchiectomy	Zoladex 3.6 mg sc Q 28 D N=128  Total or subcapsular orchiectomy N=112	Effectiveness of Zoladex depot compared with bilateral orchiectomy (total or subcapsular) in the treatment of metastatic carcinoma of the prostate  Subjective response  Objective response  Physiological effect	Subjective response Zoladex 80%  No significant difference in objective response  No significant difference bt groups for physiologic effects  Safety: Zoladex - Skin rash (3 pts) Increased bone pain (1 pt) Transient visual disturbances (2 pts) Gingival atrophy (1 pt) Diarrhea (1 pt) Orchiectomy – Scrotal contusions, hematoma, infections (8 pts)

**Table 6 (cont'd).** Review of Clinical Trials - **Goserelin vs. Orchiectomy**

TRIAL	DESIGN	INCLUSION	DOSE/THERAPY	OUTCOMES	RESULTS
Peeling et al. 1989  N = 358 pts recruited  36 recruited with daily inj of Zoladex before the depot was available  322 pts received Zoladex Depot or orchiectomy  292 evaluable	OPEN RANDOMIZED PHASE III MULTICENTER	Histologic proof of prostatic cancer; Firm evidence of metastatic disease; Life expectancy at least 3 mos; Suitable for orchiectomy; Give informed consent	Zoladex 3.6mg sc Q 28 D N = 148  Orchiectomy N = 144	Effectiveness Subjective response Objective response LH T Time to treatment failure Survival	No significant difference bt groups in subjective response  No significant difference bt groups in objective response  LH suppressed with Zoladex, but inc in orchiectomy group  T reached castrate levels during the first 4 weeks and was maintained throughout the duration; did not differ in both groups  Time to treatment failure did not differ significantly bt groups  Survival did not differ significantly bt groups
Kaisary et al. 1990  N = 358	MULTICENTER RANDOMIZED	Histologically proven metastatic cancer of the prostate with radiological and/or isotope evidence of bone metastases (or evidence of soft tissue metastases); Life expectancy of more than 3 months; Fit for orchiectomy	Zoladex 3.6mg sc Q 28 D N = 148  Orchiectomy N = 144	Subjective response  Objective response  Physiological effects of T withdrawal (hot flushes, breast swelling, breast tenderness, dec in libido and erections)  Safety	Subjective response – no significant difference bt groups Zoladex 66% Orchiectomy 73%  No statistically significant difference in objective response data  Fewer deaths in Zoladex group and median survival times in Zoladex group greater than orchiectomy group, but not statistically significant  Zoladex - T dec to 1.226 nmol/L after 4 weeks and remained suppressed for duration of treatment; LH dec to 1.47 IU/L by week 4 and remained suppressed for duration of treatment  Orchiectomy – Mean serum T dec to 0.91 nmol/L by week 4; LH inc to 20.8 IU/L at week 4 and remained elevated  No serious adverse effects to Zoladex and no local reactions  Scrotal infections at operation site in Orchiectomy group

**Table 6 (cont'd).** Review of Clinical Trials - **Goserelin vs. Orchiectomy**

TRIAL	DESIGN	INCLUSION	DOSE/THERAPY	OUTCOMES	RESULTS
Soloway et al. 1991 N=164	MULTICENTER RANDOMIZED	Histologically confirmed adenocarcinoma of the prostate; Jewett Stage D2 disease with hormonal therapy indicated as primary treatment; Measurable or evaluable disease; Life expectancy of > 3 months; Recovery from definitive local tumor complications; Without evidence of significant infection or effects or major surgery; Written informed consent given voluntarily	Zoladex 3.6 mg sc Q 28 D N = 81  Orchiectomy N = 83  Median follow-up time 210 days;  Maximum follow-up time 462 days	Endocrine response  Subjective response  Objective response  Efficacy Time to treatment failure Time to disease progression  Safety (adverse events)	Endocrine – No significant differences bt groups Median serum T reduced to castrate levels (< 50ug/dL) at week 4 in both groups and remained suppressed for 60 weeks  Efficacy No significant difference in objective response p=0.61 Zoladex 81% Orchiectomy 78%  Distribution of time to treatment failure not significantly different (p=0.55)  Distribution of time to disease progression not significantly different (p=0.22)  Safety Hot Flashes - Zoladex 53% Orchiectomy 39%

**Table 7. Review of Clinical Trials-Leuprolide SC vs DES and Depot Formulation**

TRIAL	DESIGN	INCLUSION	DOSE/THERAPY	OUTCOMES	RESULTS
Leuprolide Study Group 1984 N= 199	Phase III, multicenter, open label, randomized, cross-over	Stage D2 No previous systemic therapy	Leuprolide 1mg SC daily Or DES 3mg PO daily FOR 24 WEEKS  Median duration of treatment was 72 weeks for Leuprolide (5-114) and 73 weeks for DES (2-114)	<ul style="list-style-type: none"> <li>Clinical (objective) response</li> <li>Hormonal response</li> <li>Survival variables</li> <li>Adverse effects</li> </ul>	<ul style="list-style-type: none"> <li>Objective response (CR+PR+SD) Leuprolide – 86% DES 85%</li> <li>Hormonal Response Leuprolide –delay in fall of testosterone week 1 (p&lt;0.01); then no difference in values Both: castration levels (&lt;50ng/ml) after weeks 2 or 3 Prostatic Acid Phosphatase:decreased in both &gt;25%</li> <li>Adverse Events Hot flashes-↑ incidence with leuprolide Gynecomastia/breast tenderness- ↑ incidence with DES Nausea/vomiting- ↑ incidence with DES CV- ↑ incidence with DES 1° peripheral edema</li> <li>Survival TTFirst Progression (median) Leuprolide – 60 weeks DES – 61 weeks NSS Overall Survival (1 year) Leuprolide – 87% DES – 78% NSS</li> </ul>
Sharifi 1985 N= 25	Randomized, open label	Stage D2 No previous systemic therapy	Leuprolide 1mg SC daily Or DES 3mg PO daily FOR 60 WEEKS	<ul style="list-style-type: none"> <li>Objective response</li> <li>Hormonal response</li> <li>Subjective response</li> <li>Adverse events</li> </ul>	<ul style="list-style-type: none"> <li>Objective response (CR + PR) Leuprolide 54.5% DES 50%</li> <li>Hormonal response ↑ testosterone levels thru week 4 in leuprolide patients , both groups similar after week 4 Prostatic acid phosphatase:normal by wk12 in responders</li> <li>Subjective response Similar in each group after week 4 Disease flare in 27.3% of leuprolide pts</li> <li>Adverse Events Serious reactions more common with DES(MI, DVT, PVC's, gynecomastia, nausea, pitting edema) Leuprolide- vasomotor flushing most frequent; one MI and 2 DVT's (at high risk prior to leuprolide)</li> </ul>
Sharifi and the Leuprolide Study Group 1990 N=53	Phase III, multicenter, open label	Stage D2 No previous systemic therapy	Leuprolide depot 7.5mg IM every 4 weeks f FOR 24 WEEKS Compare to historical data using 1mg SC daily	<ul style="list-style-type: none"> <li>Safety</li> <li>Efficacy</li> </ul>	<ul style="list-style-type: none"> <li>Efficacy Testosterone- castrate levels by week3-4; initial increase in levels peaking on day 4 Prostatic acid phosphatase: &gt;25% reduction wk 12-24 Exclusions: 2 for protocol violation and 1 for irregular visits Progression in 8 (18.2%) by week 24 (similar to SC daily injections)</li> <li>Safety Adverse Events Hot flashes 57%</li> </ul>

					Sweating 10.7% >5% - peripheral edema, pain, constipation, dyspnea, chest pain, impotence, urinary frequency No worsening of symptoms in first 2 weeks
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**Table 8. Clinical Trial Results- Leuprolide Implant**

TRIAL	DESIGN	INCLUSION	DOSE/THERAPY	OUTCOMES	RESULTS
Fowler 2000 N=51	Multicenter, open-label dose ranging study	Stages A2, B, C, D1, and D2	Group 1- leuprolide implant 65mg for 12 months x1 cycle Group 2- leuprolide implant 65mg for 12 months x 2 cycles	<ul style="list-style-type: none"> <li>Efficacy</li> <li>Safety</li> </ul>	<ul style="list-style-type: none"> <li>Efficacy Testosterone decreased below castrate level in 100% between weeks 2 and 4 and remained there thru week 60 No transient increase when new implant inserted at start of year 2 in Group 2 PSA at 12 months decreased by 84% and 91% in Groups 1 and 2, respectively</li> <li>Safety Vasodilation 74.5% Bruising at insertion site 18.5% and 25% in Groups 1 and 2, respectively Infection/inflammation at insertion site in 3; resolved with po antibiotics</li> </ul>
Fowler 2000 N=80	Multicenter, Open label	Stages A2(2.5%), B(37.5%), C(38.8%), D1(11.3%), and D2(10%) No prior systemic therapy	Leuprolide implant 65mg	<ul style="list-style-type: none"> <li>Efficacy</li> <li>Safety</li> </ul>	<ul style="list-style-type: none"> <li>Efficacy Testosterone levels decreased below castrate level in 99% by week 2-4 and remained there thru the study period</li> <li>Safety Hot flashes 63.8% Bruising at insertion site 40%</li> </ul>
Fowler 2001 N=80	Multicenter, Open label Phase III	Men with untreated biopsy-proven prostate cancer; PSA level of 6.0 ng/mL or greater; PSA of 4.0ng.mL or greater after radical prostatectomy; PSA of 6.0ng/mL or greater or with a 50% increase in the PSA level from a nadir of greater than 2.0 ng.mL after radiation therapy	At 24 and 52 weeks after implantation, pts were surveyed to rate satisfaction with implant -10 questions -responses measured on 5-point Likert-Type scale  Before implantation and at 12, 24, 36, and 52 weeks after implantation, pts rated general HRQOL using SF-36	<ul style="list-style-type: none"> <li>QOL</li> </ul>	<ul style="list-style-type: none"> <li>&gt; 90% were extremely satisfied or satisfied with the overall treatment</li> <li>No changes found in summary scores of the mental and physical aspects of the SF-36 during treatment</li> </ul>

**Table 9.** Review of Clinical Trials- **Leuprolide in Atrigel**

TRIAL	DESIGN	INCLUSION	DOSE/THERAPY	OUTCOMES	RESULTS
Jackson 2000 ABSTRACT N=120	Interim report on 51 Open-label	Jewett Stage C & D (TMN = T3 & T4)	Leuprolide acetate 7.5mg in ATRIGEL® SC in abdomen every 28 days for 6 months	<ul style="list-style-type: none"> <li>• Efficacy: suppression of testosterone (T)</li> <li>• Safety</li> <li>• 2°: PSA</li> </ul>	<ul style="list-style-type: none"> <li>• Mean baseline T= 349.2mg/ml Day 3 T= 597.4ng/ml Day 28 T= 20.19ng/ml 6 month T= 6.6ng/ml &lt;10ng/ml in 82% 10-20ng/ml 16% 1 patient at 26ng/ml Once reached, no breakthroughs</li> <li>• Mean baseline PSA=21.6ng/ml 6 month PSA mean= 1.2ng/ml ≤4ng/ml in 94.1% &gt;4ng/ml to &lt;10ng/ml in 4% 1 patient at 13.4ng/ml</li> <li>• AE: Pain at injection site, mild, lasting 15-30 seconds Hot flashes/flushes mild</li> </ul>
Jackson 2001 ABSTRACT N=117	Open label	Jewett Stage A, B, C, D	Leuprolide acetate 22.5mg in ATRIGEL® SC in abdomen every 3 months for six months	<ul style="list-style-type: none"> <li>• Efficacy: suppression of testosterone (T)</li> <li>• Safety</li> <li>• 2°: PSA</li> </ul>	<ul style="list-style-type: none"> <li>• Mean baseline T=367.1ng/ml Median of 21 days to T&lt;50ng/ml 6 month T= 10.0±0.7ng/ml &lt;10ng/ml 62% 10-20ng/ml 32% &gt;20ng/ml and ≤50ng/ml 6% 1 breakthrough after castrate level</li> <li>• Mean PSA=86.4ng/ml±517.9ng/ml 6 mos PSA= 1.7ng/ml ±5.5ng/ml ≤4ng/ml in 93.1%</li> <li>• AE: Burning/stinging at injection site for 15-30seconds Hot flashes/flushes mild</li> </ul>

**Table 10.** Review of Clinical Trials- **Triptorelin**

TRIAL	DESIGN	INCLUSION	DOSE/THERAPY	OUTCOMES	RESULTS
DEB-96-TRI-01 PHASE 1 Unpublished  N= 346	PHASE 3, MULTICENTER, OPEN-LABEL, CONTROLLED, RANDOMIZED	-Histologically proven prostate cancer, T3-4NxMx, or TxN1-3Mx, or TxNxM1 (TNM Classification) -A recent bone scan within the previous 3 months -Serum testosterone levels > 5nmol/L -Karnofsky performance index > 40 -Expected survival of $\geq$ 12 months -Absence of another malignancy, other than dermatological, for 5 years -Written, informed consent given before entry into the study	Triptorelin Depot 3.75mg IM q 28 days x 9 doses N=172  Triptorelin LA 11.25mg IM q 84 days x 3 doses N=174	To demonstrate that the 84-day formulation of triptorelin was not inferior to the 28-day formulation as assessed by: <ul style="list-style-type: none"> <li>The proportion of patients achieving castrate levels of serum testosterone (testosterone <math>\leq</math> 1.735 nmol/L) on Study Day 29;</li> <li>The proportion of patients maintaining castrate levels of serum testosterone from Study Day 57 through Study Day 253</li> </ul>	<ul style="list-style-type: none"> <li>From IIT Population <p><b>84-day formulation:</b> Mean baseline T=11.24nmol/L Day 29=0.28 nmol/L (<math>\pm</math>0.88) Day 57-253=0.16nmol/L (<math>\pm</math>0.19) – 0.43 (<math>\pm</math>1.48) T levels within castrate levels on Day 29 = 97.7% T levels within castrate levels on Days 57-253 = 94.4%</p> <p><b>28-day formulation:</b> T=12.31nmol/L Day 29=0.54 nmol/L (<math>\pm</math>1.41) Day 57-253=0.19nmol/L (<math>\pm</math>0.22) – 0.38 (<math>\pm</math>2.04) T levels within castrate levels on Day 29 = 92.7% T levels within castrate levels on Days 57-253 = 94.2%</p> </li> <li>From PP Population <p><b>84-day formulation:</b> T levels within castrate levels on Day 29 = 97.6% T levels within castrate levels on Days 57-253 = 94.1%</p> <p><b>28-day formulation:</b> T levels within castrate levels on Day 29 = 92.5% T levels within castrate levels on Days 57-253 = 95.3%</p> </li> <li>Breakthrough T as assessed from subset of 30 patients (15 in each tx group) 84-day formulation: 13% 28-day formulation: 0%</li> <li>Adverse Events (<math>\geq</math>10%): Hot flushes, headache, skeletal pain, back pain, constipation, viral infection, dysuria, arthralgia, pain, hypertension, coughing, leg pain, and urinary tract infection</li> </ul>

**Table 10 (cont'd). Review of Clinical Trials- Triptorelin**

DEB-96-TRI-01 PHASE 2 Unpublished N=285 Safety N=284 ITT N=277 PP N=272	PARALLEL GROUP RANDOMIZED CONTROLLED MULTICENTER PHASE III	-Stage C or D -Histologically proven prostate cancer, T3-4NxMx, or TxN1-3Mx, or TxNxM1 (TNM Classification) -A recent bone scan within the previous 3 months -Serum testosterone levels > 5nmol/L -Karnofsky performance index > 40 -Expected survival of ≥ 12 months -Absence of another malignancy, other than dermatological, for 5 years -Written, informed consent given before entry into the study	Triptorelin Depot 3.75mg IM q 28 days x 9 doses N= 140 Leuprolide Acetate 7.5 mg IM q 28 days x 9 doses N=144	<p><b>PRIMARY OBJECTIVE</b>                  To demonstrate that the 1-month formulation of triptorelin was as effective as the to the 1-month formulation of leuprolide as assessed by:</p> <ul style="list-style-type: none"> <li>The proportion of patients achieving castrate levels of serum testosterone (testosterone ≤ 1.735 nmol/L) on Study Day 29;</li> <li>The proportion of patients maintaining castrate levels of serum testosterone from Study Day 57 through Study Day 253</li> </ul> <p><b>SECONDARY OBJECTIVE</b>                  Assess the absence of triptorelin accumulation based on pre-injection levels and compare triptorelin pamoate and leuprolide acetate in terms of:</p> <ul style="list-style-type: none"> <li>Absence of gonadotropin stimulation (LH and FSH), assessed at 0 and 2 hours post-injection on Days 85 and 169.</li> <li>Regression in bone pain from baseline to end of treatment</li> <li>Median change in PSA from baseline to end of treatment</li> <li>Median change in QOL scales from baseline through treatment</li> <li>Testosterone pharmacodynamics for 24 hours in a subset of pts following the injection of each formulation on Day 85</li> </ul> <p><b>SAFETY</b></p> <ul style="list-style-type: none"> <li>Incidence of clinical adverse events</li> <li>Nine month survival</li> <li>Vital signs and lab parameters</li> <li>Local tolerance at injection site</li> </ul>	<table border="1" data-bbox="1430 126 2013 329"> <thead> <tr> <th></th> <th>% Pts on Leu with T &lt; castration level</th> <th>% Pts on Trp with T &lt; castration level</th> </tr> </thead> <tbody> <tr> <td>Day 29</td> <td>99.3</td> <td>91.2</td> </tr> <tr> <td>Day 57</td> <td>97.1</td> <td>97.7</td> </tr> <tr> <td>Cum. Maint. (Months 2-9)</td> <td>93.1</td> <td>96.1</td> </tr> </tbody> </table> <p>Cannot be concluded that Trp is at least as effective as Leu with respect to achievement of castration on day 29 since lower limit of 95% CI is not above -10%.</p> <p>Can be concluded that Trp is at least as effective as Leu in maintaining castration during months 2-9</p> <p>No accumulation of Trp occurred after a 9-month administration</p> <p>No clinically significant inc in LH or FSH in both treatment groups post-dose on Days 85 and 169</p> <p>Mean reduction in PSA by Day 253:                  97.1% - Triptorelin                  97.0% - Leuprolide</p> <p>Bone pain, analgesic use, and QOL similar in both groups (no quantitative data presented)</p> <p>0 Pts with T &gt; castrate (&gt;1.735nmol/L) in Trp Group                  3 Pts with T &gt; castrate (&gt;1.735nmol/L) in Leu Group</p> <p>Most frequently reported adverse events</p> <table border="1" data-bbox="1430 865 2013 1019"> <thead> <tr> <th></th> <th>% Reported with TRP</th> <th>% Reported with LEU</th> </tr> </thead> <tbody> <tr> <td>Hot Flushes</td> <td>58.6</td> <td>54.2</td> </tr> <tr> <td>Skeletal Pain</td> <td>21.4</td> <td>16.7</td> </tr> <tr> <td>Headache</td> <td>13.6</td> <td>18.8</td> </tr> <tr> <td>Constipation</td> <td>15.0</td> <td>15.3</td> </tr> </tbody> </table> <p>Statistically significant difference in 9-month survival rate                  Trp – 97.0%                  Leu – 90.5%</p> <p>No statistically significant difference in lab data or vitals.</p> <p>Local tolerance</p> <table border="1" data-bbox="1430 1179 2013 1406"> <thead> <tr> <th></th> <th>% Reported with TRP</th> <th>% Reported with LEU</th> </tr> </thead> <tbody> <tr> <td>Swelling</td> <td>0.7 (Days 1 and 2) 1.6 (Days 85 and 169)</td> <td>3.0 (Day 85) 0.8 (Day 169)</td> </tr> <tr> <td>Bruising</td> <td>2.9 (Day 1) 3.1 (Day 85)</td> <td>2.8 (Day 1) None (Day 85)</td> </tr> <tr> <td>Pain</td> <td>3.6 (Day 1) 3.1 (Day 85) 4.1 (Day 169)</td> <td>0.7 (Day 1) 2.2 (Day 85) 1.6 (Day 169)</td> </tr> </tbody> </table>		% Pts on Leu with T < castration level	% Pts on Trp with T < castration level	Day 29	99.3	91.2	Day 57	97.1	97.7	Cum. Maint. (Months 2-9)	93.1	96.1		% Reported with TRP	% Reported with LEU	Hot Flushes	58.6	54.2	Skeletal Pain	21.4	16.7	Headache	13.6	18.8	Constipation	15.0	15.3		% Reported with TRP	% Reported with LEU	Swelling	0.7 (Days 1 and 2) 1.6 (Days 85 and 169)	3.0 (Day 85) 0.8 (Day 169)	Bruising	2.9 (Day 1) 3.1 (Day 85)	2.8 (Day 1) None (Day 85)	Pain	3.6 (Day 1) 3.1 (Day 85) 4.1 (Day 169)	0.7 (Day 1) 2.2 (Day 85) 1.6 (Day 169)
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