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APPROVAL PACKAGE FOR:

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20-715

Medical Review(s)

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NDA 20 715 Amendment
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MEDICAL OFFICER REVIEW OF NDA AMENDMENT
Complete Response to Non-Approval Letter Of June 26, 1997

Drug product – triptorelin pamoate for injectable suspension
Drug name – TRELSTAR® Depot 3.75 mg
Drug class – synthetic GnRH competitive agonist
Dose and route – 3.75 mg depot dose intramuscular q 28 days
Indication – palliative treatment of advanced prostate cancer
Sponsor – Debio Recherche Pharmaceutique S.A.
Martigny, Switzerland
U.S. Representative – Robert J. McCormack, Ph.D.
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1. Summary

TRELSTAR® is a synthetic GnRH competitive agonist, formulated as microgranules of triptorelin pamoate and intended to deliver a depot dose of drug over a one-month treatment interval. The product is indicated for the palliative treatment of men with advanced prostate cancer.

The safety of this product was evaluated in 357 patients with histologically-confirmed adenocarcinoma of the prostate. Patients received triptorelin pamoate 3.75 mg monthly for up to 9 months. Safety endpoints included adverse events, vital signs, laboratory tests, concomitant medications, and an evaluation of local tolerability. Review of the safety database identified no safety concerns that would prevent approval of this product.

The primary efficacy study of this product was a randomized, open-label, active-control trial in 137 patients who received triptorelin pamoate 3.75-mg depot. The 140 patients in the active control arm received leuprolide acetate, 7.5-mg depot. The basis for assessment of efficacy was the rate of success of the drug in achieving medical castration [serum testosterone < 1.735 nmol/L] by day 29 and maintaining castrate levels during the nine months of use. In addition, the product was evaluated for the incidence of 'acute-on-chronic' phenomenon with repeat dosing. Supportive efficacy data was provided in a study of 164 patients receiving triptorelin pamoate 3.75-mg depot for up to nine months. This patient population was identical to that of the primary efficacy trial. The efficacy endpoints for this trial were the same as for the randomized, active-control study.

Review of the efficacy data submitted showed that TRELSTAR® demonstrated efficacy at rates similar to the performance of both the active comparator in the current submission and to other GnRH agonist products currently approved and marketed for similar indications.

From a clinical perspective, this product is safe and effective and a recommendation for approval has been made.

2. Regulatory history

TRELSTAR® depot 3.75 mg [triptorelin pamoate] was originally developed under an IND [redacted] submitted by Lederle Laboratories June 1986. [redacted] In June 1994 Debio R.P. became the sponsor of the drug and continued development of the drug for the indication of advanced prostate cancer. In meetings with the Division of Metabolic and Endocrine Drug Products the sponsor proposed the submission of three completed European studies comparing triptorelin acetate with orchiectomy for treatment of advanced prostate cancer. In none of the studies was "achievement and maintenance of castrate levels of testosterone"

specified as the primary efficacy endpoint when the study was initiated. The NDA was filed and accepted for review in June 1996.

On clinical review, a responder analysis for the primary efficacy endpoint of achievement of castrate levels of testosterone at one month and maintenance of castrate levels without escape through month 24 was performed for study drug and orchiectomy patients. In these three studies, 27.8%, 47.5% and 52.4% of triptorelin acetate patients were classified as "successes". The success rates for the patients in the orchiectomy arms were 18.2%, 74.4%, and 66.7%. The reviewer concluded that neither the sponsor's analysis or the re-analysis by the Division supported the efficacy of triptorelin for the treatment of advanced prostate cancer.

The reviewer reported that, on review of the safety data provided in the original NDA, triptorelin acetate appeared to demonstrate a safety profile similar to other GnRH agonists. However, the sponsor reported that, in the worldwide post-marketing experience with triptorelin, "three cases of anaphylactic shock and two cases of angioedema have been reported". No hypersensitivity adverse events were identified in the NDA population, although the reviewer comments that "because of inadequate data one cannot determine whether some of the deaths in this study were secondary to anaphylaxis."

Deficiencies were also identified by the biopharmaceutics, chemistry, and microbiology reviewers. A non-approval letter sent to the sponsor on June 26, 1997.

In a meeting with the Division September 9, 1997 the FDA staff suggested that resolution of the clinical deficiencies would require one well controlled study that:

- was adequately powered to rule out a clinically significant difference between triptorelin pamoate and an active comparator [currently marketed GnRH agonist]
- was of at least nine months duration in order to establish an adequate safety database
- had co-primary efficacy endpoints of 1) achievement of castrate levels of testosterone within 28 days, and 2) maintenance of castrate levels of testosterone without escape through the treatment period
- had secondary clinical endpoints such as survival and reduction in bone pain or other evidence of morbidity.

The "first phase" portion of the study DEB-96-TRI-01 was ongoing at the time of the non-approval of the original NDA filing in June 1997. The study was originally intended to compare the efficacy of the three-month depot formulation to the one-month formulation. The primary efficacy endpoint was the achievement of suppression of serum testosterone to castrate levels within 28 days and the maintenance of castration over the duration of a nine-month treatment interval.

After meeting with the Division, the sponsor proposed that the study enrollment be closed, with data from patients currently in the to-be-marketed triptorelin pamoate 1-month arm used to support the primary efficacy endpoint of achievement and maintenance of castration.

In October 1997 the sponsor submitted an amendment to the IND and NDA to add a "second phase" for the same study. The amended study continued the initial study of the two triptorelin pamoate formulations but terminated further enrollment and accrual of 3-month depot patients. This original population, anticipated to be about 360 total patients, would represent the "first phase" of the proposed two-phase study.

Using a study design very similar to the first phase, the to-be-marketed triptorelin pamoate 1-month formulation was to be compared to leuprolide acetate 7.5-mg depot dose in the second phase. Both medications, administered every 28 days would be continued for a nine-month treatment duration to assess the ability of the study drug to achieve medical castration by day 29 and maintain castrate levels, without escape, over the duration of treatment.

The enrollment criteria proposed were the same for the second phase patients as for the first phase patients. The sponsor proposed that at least 460 patients be included in the total study, 180 patients in the first phase receiving triptorelin pamoate 1-month formulation and an additional 280 subjects in the second phase comparison randomized 1:1 to either triptorelin pamoate 1-month or leuprolide. The population enrollment targets were based on a power analysis calculation.

The sponsor anticipated completing enrollment in the second phase of the trial by September 1998, with the last patient completing the nine-month treatment interval by July 1999. The two phases of the trial would not have any common patients. The two phases would run concurrently.

The complete response to the NDA non-approval letter of June 26, 1997 was submitted on December 16, 1999.

The current submission contained 103 volumes. The volumes reviewed for this clinical review included volumes 1, 21 through 59, and 96 through 103.

3. Clinical Background

The use of orchiectomy as a means of castration for treatment of advanced prostate cancer has been an accepted and standard treatment of adenocarcinoma of the prostate since the seminal work of Charles Huggins in the 1940's and 1950's. The procedure was felt to offer palliation for those patients who were demonstrating either local or systemic effects of their prostate cancer—local obstruction at the bladder outlet or of

the ureters or systemic complaints of aesthenia, weight loss, or bone pain. No studies have shown that castration will cure this cancer or prolong survival.

Until 20 years ago, the use of estrogenic compounds, generally oral estrogen as diethlystilbestrol [DES], was often offered as an alternative to surgical castration. The dose of estrogen used varied widely in clinical practice, from intravenous doses of 500 mg of stilphostrol to the use of 1 to 100 mg of oral estrogen as DES. The most commonly prescribed dosage of DES had been a 5 mg single daily dose. The Veterans Administration Cooperative Urological Group [VACURG] studies of the 1960's reported an increased incidence of cardiac, thrombophlebotic, and thromboembolic adverse events [AEs] in patients treated with DES 5mg for this indication. Patients also reported gynecomastia and GI adverse reactions on DES 5 mg. The second study of the VACURG series demonstrated that 1 mg of DES was as effective as the 5 mg dose and did not produce the AEs noted at 5 mg. Nevertheless, DES 3 mg became the "accepted dose" when another study reported that the 3 mg dose reliably produced castrate levels of testosterone. A trial of 1 mg DES versus 3 mg was never done to determine whether the lower dose could match placebo, orchietomy, or DES 3 mg in efficacy and safety.

The lack of appeal to many patients of surgical castration and the adverse effects of estrogen therapy lead investigators to pursue alternative methods of reversible medical castration.

The production of testosterone by the Leydig cells of the testes is regulated by the release of LH by the anterior pituitary gland. Blocking the release of LH will decrease production of testosterone. The decapeptide hormone GnRH, produced in the hypothalamus, controls LH release. The development of synthetic analogues of GnRH with a greater affinity for receptors in the pituitary has allowed their use as *competitive agonists*, blocking the release of LH, and decreasing testosterone production to castrate levels.

In December 1983, the synthetic gonadotropin-releasing hormone [GnRH], leuprolide acetate, was submitted as NDA 19 010 [TAP Pharmaceuticals]. The primary clinical trial, study M81-017, was offered to support the registration of this first synthetic GnRH agonist for the palliative treatment of advanced prostate cancer.

The study compared leuprolide acetate, 1 mg as a daily subcutaneous dose against DES, 1-mg tid oral dose. The population studied was men with symptomatic stage D2 adenocarcinoma of the prostate with measurable metastatic disease. The evaluable population included 92 patients [initial leuprolide treatment] and 94 patients [initial DES treatment]. The study design was a conditional crossover design. Patients were switched from one treatment arm to the alternative treatment for either progression or intolerable side effects. No blinding of investigators or subjects was done. The primary efficacy endpoint was the rate of objective favorable response by National Prostate Cancer Project [NPCP] criteria. Treatment failure was defined as either objective progression of metastatic disease or intolerable side effects.

Objective favorable response (either complete response [CR], partial response [PR] or no change [NC] by NPCP criteria) for the leuprolide group was recorded for 79 of 92 patients and for 80 of 94 DES patients. Ten of 92 patients in the leuprolide group and 2 of 94 patients in the DES group had evidence of objective progression by NPCP criteria. Three of 92 patients in the leuprolide group and 12 of 94 patients in the DES group were categorized as failures for "other" reasons, usually intolerable side effects.

Leuprolide acetate [Lupron™ 1 mg; TAP Pharmaceuticals] was approved 9 April 1985 for the palliative treatment of advanced prostatic cancer. The opinion of the oncology advisory committee and the division director was that this therapy was "second-line" treatment in men in whom surgical castration or estrogens were not indicated or not acceptable to the patient.

The first depot dose of Lupron was approved [NDA 19 732] in January 1989 as a 7.5 mg dose administered every 28 days. In study M85-097, the testosterone suppression rate achieved at week 4 for this formulation was reported as 91%.

The three month depot Lupron, 22.5 mg and four month depot, 30 mg were approved December 1995 [NDA 20517] and May 1997 [NDA 20517, S-002]. The testosterone suppression rate at week 4 in these three registration studies were reported as 92%, 97%, and 94%. No confidence intervals were reported.

Lupron depot, 1-month, 3-month, and 4-month formulations, are labeled as indicated in the palliative treatment of advanced prostatic cancer as an alternative treatment of prostatic cancer when orchiectomy or estrogen administration are either not indicated or unacceptable to the patient.

Rationale for the development of triptorelin pamoate - The drug is a synthetic decapeptide, an analog of the naturally occurring luteinizing hormone releasing hormone [LHRH] and differing from LHRH by only one peptide. While LHRH has an L-glycine at the position 6, triptorelin pamoate has a substituted D-tryptophan. Other currently marketed synthetic agonists-leuprolide and goserelin- have other peptide substitutions at this same position. The sponsor claims that the substitution in triptorelin pamoate results in increased resistance to cleavage by enzymes and increases the biological potency compared to natural LHRH. In vitro studies have suggested that triptorelin pamoate is approximately 100 times more potent that LHRH.

Over the past ten years the sponsor has marketed triptorelin as a pamoate salt in a lyophilized microgranule formulation for one-month depot dosing. The sponsor states that the pamoate salt, compared to the acetate formulation, has the advantage of not requiring [redacted] in the manufacturing process and can be stored at room temperature.

Foreign Marketing experience – Triptorelin is marketed, as the acetate or pamoate salt, in over 60 countries for treatment of advanced prostate cancer. The sponsor reports that, in no instance, has a licensing application been denied on the basis of safety concerns. The pamoate formulation is approved for use as a 3.75 mg lyophilized microgranule product in Canada, Mexico, Sweden, Switzerland and a number of South American countries. The first approval of triptorelin pamoate 3.75 mg microgranule formulation was in Brazil in 1991.

Approximately [redacted] vials of triptorelin, as either the acetate or pamoate salt in immediate release or depot formulations, were sold over the ten-year period from 1987 through the first quarter 1998.

4. Summary of NDA Clinical Section

Overview and efficacy endpoints

The clinical section of the NDA includes one large phase III, open-label, randomized, active-control multicenter trial, study DEB-96-TRI-01, and two small, non-comparative, short duration supportive trials, DEB-96-TRI-02 and DEB-98-TRI-01.

The original study design of DEB-96-TRI-01 was amended one year after study initiation in order to change the active-control drug in the comparator arm from triptorelin pamoate 11.25 mg 3-month depot to leuprolide acetate 7.5 mg 1-month depot.

The first phase of this study provides supportive efficacy and safety data on approximately 180 patients with advanced adenocarcinoma of the prostate receiving triptorelin pamoate 1-month depot formulation for up to nine months. Patients in the active control arm of this first phase received the 3-month triptorelin pamoate formulation.

The second phase of this study provides the primary efficacy and safety data for evaluating the approvability of the drug. One hundred forty patients in the safety population with advanced adenocarcinoma of the prostate received triptorelin pamoate 1-month depot formulation for up to nine months. Patients in the active control arm of this second phase received leuprolide acetate 7.5 mg depot formulation monthly for up to nine months.

Trials DEB-96-TRI-02 and DEB-98-TRI-01 offer further supportive safety data and limited efficacy data for 32 and 13 patients, respectively, with advanced adenocarcinoma of the prostate, treated with two doses of triptorelin pamoate 1-month depot formulation and followed for 56 days and 29 days, respectively.

In all trials, the primary efficacy endpoint was defined as the achievement of testosterone suppression by day 29 and the maintenance of suppression over nine months without escape from suppression. The secondary efficacy endpoint, avoidance of 'acute-on-chronic' flare, was defined as an increase of serum LH to < 1.0 IU/L at 2 hours after repeat triptorelin pamoate administration. This was measured in a subset of 15 patients in the first phase and in all patients in the second phase of DEB-96-TRI-01. All 32 patients in study DEB-96-TRI-02 had measurement of serum LH at zero, 2, 4, and 6 hours after administration of triptorelin pamoate on days zero and 28.

Safety endpoints

Standard safety endpoints included adverse events, vital signs, concomitant medications and laboratory results. Deaths and withdrawals due to adverse events were described in narrative format. Tolerability and local reactions from the intramuscular injection of triptorelin pamoate were evaluated.

5. Clinical Trial DEB-96-TRI-01 [First Phase]

Study overview – This study was conducted at 19 centers in South Africa. The principal investigator was Professor C Heyns, Department of Urology, University of Stellenbosch, Cape Town, South Africa. The first patient enrolled 27 January 1997 and the last patient completed the study 4 September 1998.

Study objectives - The first phase of DEB-96-TRI-01 was originally intended to demonstrate the equivalence of the to-be-marketed triptorelin pamoate 1-month and triptorelin pamoate 3-month formulations in ability to:

- Achieve castrate levels of serum testosterone [< 1.735 nmol/L] within 29 days following intramuscular injection, and;
- Maintain castrate levels of serum testosterone from months 2 through 9 of treatment

Secondary objectives - The sponsor proposed to assess the presence of an acute-on-chronic "flare" phenomenon, the transient increase in LH that may occur during the first 24 hours following the repeat dosing of synthetic GnRH competitive agonists. LH and FSH levels were to be obtained at zero hours and two hours post-injection on days 85 [month 3] and 169 [month 6].

Other secondary objectives include the assessment of change from baseline in bone pain symptoms, change from baseline in PSA levels, and change from baseline in quality-of-life measures.

Safety objectives - The sponsor stated that the 1-month and 3-month formulations were compared for:

- Incidence of clinical adverse events
- Survival
- Vital signs and laboratory test results

Patient population - Patients eligible for enrollment in the study had histologically proven adenocarcinoma of the prostate, stage $T_{3-4}N_xM_x$, $T_xN_{1-3}M_x$, or $T_xN_xM_1$ by the TNM classification. Other inclusion criteria included:

- Bone scan within three months of enrollment
- Serum testosterone level > 5 nmol/L
- Karnofsky performance index > 40
- Expected survival of > 12 months
- Absence of another malignancy, other than dermatological, for > 5 years

Patients were excluded from participation for:

- Prior hormonal treatment for prostate cancer, including use of finasteride
- Presence of another malignancy
- Prior hypophysectomy or adrenalectomy
- Known or high suspicion of vertebral metastases from prostate cancer
- Impaired renal function with serum creatinine > 2x upper limit of normal [ULN]
- Impaired hepatic function with AST or ALT > 3x ULN
- Recent or concurrent use of drugs known to affect the metabolism or secretion of androgenic hormones
- Use of anticoagulants

There were no restrictions on the age of patients enrolled in this study.

Study design - The first phase of DEB-96-TRI-01 was a parallel-group, randomized, active-control, multicenter study of two depot formulations of triptorelin pamoate for the treatment of patients with advanced adenocarcinoma of the prostate. The 1-month formulation contains 3.75 mg of triptorelin pamoate and the 3-month formulation contains 11.25 mg of triptorelin pamoate.

Study duration – Both the study drug and the active control formulation were administered by intramuscular injection every 28 days for nine months [253 days].

Primary outcome variables

Efficacy variables - The primary efficacy measure in the first phase was serum testosterone levels, obtained every 28 days. Secondary variables included serum LH, FSH, triptorelin, and PSA levels. Bone pain was assessed by a visual analog scale rating and by a count of analgesic use. Quality of life was assessed by the use of a questionnaire instrument.

Safety variables – The primary safety measure was the self-reporting of adverse events by WHO classification. Other variables included survival, vital signs, and laboratory results. Clinical chemistry, hematology, and coagulation studies were obtained.

Efficacy Endpoints

The co-primary efficacy endpoints were both the rate of achieving medical castration [serum testosterone < 1.735 nmol/L] by day 29 and the rate of maintaining medical castration at all data points monthly from month 2 to month 9.

Secondary efficacy endpoints included the rate of LH flare at the time of repeat dosing at months 3 and 6 as measured by the percentage of patients maintaining an LH of < 1.0 IU/L at two hours after repeat dose.

Other secondary endpoints include change from baseline in bone pain, change from baseline in serum PSA levels, and change from baseline in quality-of-life as assessed by a questionnaire measuring function and symptoms.

Safety endpoints

The primary safety endpoint was adverse events, assessed at all study visits using World Health Organization classification. Laboratory measures of clinical chemistry and hematology values were obtained at baseline and days 85, 169, and end of study at day 253. Vital signs—blood pressure, heart rate, and temperature—and body weight were recorded at each visit. At visits on days 0, 85, and 169 vital signs were measured at two and four hours post-injection.

Tolerance or local reaction to injection of study drug was evaluated at baseline and on days 85 and 169.

Conduct of the study – During the pre-study screening interval, potential patients were evaluated for eligibility based on inclusion/exclusion criteria. Medical history and physical examination, review of performance status, serum testosterone levels, bone scan results within three months, and clinical laboratory findings were performed. After informed consent was obtained, patients were randomized to either triptorelin pamoate or leuprolide. Randomization was stratified by center and balanced between the two treatment arms.

Statistical Analysis Plan

Efficacy analysis - The sponsor evaluated the primary efficacy variable for non-inferiority between study drug and active comparator by assessing the proportion of patients who achieved castrate levels of serum testosterone on Day 29 using two-sided 95% confidence intervals for the difference in castration rates. Maintenance

of castration was evaluated by estimating the probability of maintenance from month 2 through 9 using a Kaplan-Meyer survival analysis technique. Two-sided 95% confidence intervals were reported for the difference between treatment groups. Avoidance of "acute-on-chronic" flare at the time of dosing on days 85 and 169 was assessed by calculating the proportion of patients in each treatment group who showed a < 1.0 IU/L increase in serum LH from zero to 2 hours post-injection. A two-sided 95% confidence interval was reported for the difference between groups.

Safety analysis – Adverse events were reported by body system category and presented as summary listings of number and percentage of patients noting an event and the number of mentions of the event.

6. Clinical Trial DEB-96-TRI-01 [Second Phase]

Study overview – This study was conducted at 29 centers in South Africa. The principal investigator was Professor C Heyns, Department of Urology, University of Stellenbosch, Cape Town, South Africa. The first patient enrolled 9 January 1998 and the last patient completed the study 11 February 1999.

Study objective – The second phase of DEB-96-TRI-01 was designed to demonstrate that the to-be-marketed 1-month formulation of triptorelin pamoate was at least as effective as leuprolide in its ability to achieve medical castration on day 29 and maintain castrate levels of serum testosterone from months two through nine of treatment.

Study population - Patients eligible for enrollment in the study had histologically proven adenocarcinoma of the prostate, stage $T_{3-4}N_xM_x$, $T_xN_{1-3}M_x$, or $T_xN_xM_1$ by the TNM classification. Inclusion and exclusion criteria for the second phase were identical to those of the first phase.

Study design - The second phase of DEB-96-TRI-01 was a parallel-group, randomized, active-control, multi-center study of two depot formulations of synthetic GnRH competitive agonists for the treatment of patients with advanced adenocarcinoma of the prostate.

Study duration – Both the study drug and the active control formulation were administered by intramuscular injection every 28 days for nine months [253 days].

Primary efficacy variables and endpoints for the second phase were identical to those specified in the first phase study [see above].

Secondary efficacy endpoints for the second phase were identical to those specified in the first phase study [see above].

In addition, triptorelin pharmacokinetic measurements were determined on a subset of fifteen patients over 48 hours following the triptorelin pamoate doses on days 1, 85, 169, 197, and 225. Serum testosterone levels were drawn over the seven days following the first injection in this same subset of patients.

Statistical Analysis Plan - The statistical methods used by the sponsor in the analysis of the efficacy and safety data from the second phase were identical to those described for the first phase [see above].

Reviewer comments on study design

In response to the clinical deficiencies found on review of this NDA in 1997, the sponsor submitted an adequate study design that evaluated the co-primary endpoint - -achieving and maintaining castration- suggested in consultation with the Division. However, the timing and frequency of measurement of the outcome variables that define this endpoint differs somewhat from the measures that other sponsors have used in evaluating efficacy for this indication.

- *Achievement of castration - The DEB-96-TRI-01 study design allows for only one measurement of serum testosterone at day 29 as a measure of success in achieving castration by one month. Other similar drugs in this class have been studied with multiple serum testosterone determinations during the first two months of therapy. With this supplemental information, those patients who are not castrate on day 29 could be assessed more closely for time to castration between day 29 and day 57.*

- *Maintenance of castration - In evaluating the "maintenance of castration" co-primary efficacy endpoint for this indication, other approved drugs have shown the ability to maintain castrate levels of testosterone, without any escape, from the date of castration through three dosing cycles [e.g. through day 87 for a one-month depot formulation]. The sponsor has selected nine months as the study duration and evaluated the probability of successful maintenance from months two through nine, using a survival analysis methodology.*

- *Avoidance of flare phenomenon - A secondary efficacy endpoint of interest to the Division is the potential for the drug to produce an "acute- on-chronic" flare of testosterone with repeat dosing of the drug. The sponsor has chosen to assess this endpoint by measuring the increase in serum LH at baseline and at two hours after dosing on days 85 and 169. The sponsor defined success in avoiding a significant flare as an LH level of < 1.0 IU/L at two hours after dosing. The sponsor has not provided a rationale for selecting the two hour time point as the "best" time to study. The sponsor did not measure serum testosterone levels at these same time points. No linkage between testosterone and LH levels has been provided by the sponsor.*

This drug is a new molecular entity. The best measure of its efficacy and safety is the performance of the to-be-marketed formulation in a randomized trial with an active comparator. The study design of the second phase of the DEB-96-TRI-01 study allows for such a comparison.

Since the first phase study population is similar to that of the second phase, the sponsor has pooled the study populations from both phases of the DEB-96-TRI-01 study in reporting efficacy outcomes in an integrated efficacy analysis. However, the data from these first phase triptorelin pamoate patients should be examined independent of its inclusion in any pooled data. Review of the efficacy data from the first phase of the trial may be supportive of the efficacy outcomes found in the second phase of this study.

Secondary efficacy endpoints such as PSA levels, quality-of-life assessment, and changes in bone pain were considered exploratory in nature.

The inclusion and exclusion criteria for the patient population are similar to those used in the design of studies for other approved GnRH agonist products.

7. Supportive Studies

Clinical trial DEB-96-TRI-02

Thirty-two men with advanced prostate cancer were treated with two doses of triptorelin pamoate 3.75 mg in an open-label non-comparative trial. Serum testosterone levels were measured on day 29, before the second dose of triptorelin pamoate, and on day 56.

The 32 patients in this study had only sporadic documentation of adverse events and were not included in the population of 325 patients evaluated for adverse events in the integrated summary of safety.

Clinical trial DEB-98-TRI-01

Thirteen men with advanced prostate cancer were enrolled in an open-label, non-comparative study of triptorelin pamoate 3.75 mg microgranules. All patients received two doses of the study drug, on day one and on day 29. The primary objective of the study was the assessment of in vitro/in vivo correlation of the dissolution testing of the one-month formulation. A secondary objective was the assessment of the achievement of castrate levels of testosterone 28 days after the first dose. Serum testosterone levels were obtained for each patient at time zero, at 1, 2, 3, 4, 6, 8, 12, and 24 hours on day 1, then on days 3, 4, 5, 6, 7, 8, 14, 21, and 28. Serum

LH levels were obtained from all patients at 2, 4, and 6 hours after each dosing of triptorelin pamoate.

8. Disposition of Patients

DEB-96-TRI-01 [First phase]

Safety population - Three hundred forty-eight patients were enrolled in the first phase and randomized to either triptorelin pamoate 1-month formulation [1-mo.] or triptorelin pamoate 3-month formulation [3-mo.]. Two patients, one randomized to each arm, did not receive any study medication and were excluded from the safety population.

- **Three hundred forty-six patients were included in the safety population, 172 patients receiving triptorelin pamoate 1-mo and 174 patients receiving triptorelin pamoate 3-mo.**

Intention-to-treat population - The intention-to-treat [ITT] population was defined as all patients who received study drug and had a measurement of the primary efficacy variable, serum testosterone on day 29.

Eight patients from the triptorelin pamoate 1-mo. group were excluded from the ITT population. Seven patients failed to receive a serum testosterone determination on day 29 and one patient received the wrong study drug on day one.

Three patients from the triptorelin pamoate 3-mo. group were excluded from the ITT population because they had no primary efficacy data obtained on day 29.

- Three hundred thirty-five patients were included in the ITT population, **164 patients receiving triptorelin pamoate 1-mo.** and 171 receiving triptorelin pamoate 3-mo. The racial distribution of the triptorelin pamoate 1-mo patients was 49.4% Caucasian and 50.6% Black/Colored.

Early withdrawals from study - Of the **164 triptorelin pamoate 1-mo patients** in the ITT population, 21 patients dropped out before the termination of the study. Reasons for withdrawal were:

- Drug-related adverse event – 1
- Non-drug related adverse event – 10
- Patient lost to follow-up – 9
- Other – 1

The sponsor had specified that, in accounting for missing data in the assessment of efficacy, drop-outs would be counted as failures if the cause for withdrawal was a

drug-related adverse event and counted as successes if the cause for withdrawal was a non-drug related event or loss to follow-up with the last testosterone value at castrate levels.

Using these criteria, of the 21 patients who dropped out and had missing data, one patient was counted as a "failure" and twenty patients counted as "successes" among censored patients.

- **One hundred forty-three patients in the triptorelin pamoate 1-mo. ITT population completed day 253 [9 months] of the study.**

Protocol violations - Fifteen major and 22 minor protocol violations were reported in the 164 patients receiving triptorelin pamoate 1-mo. The fifteen major violations included:

- Out of schedule drug administration – 8
- Inclusion/exclusion criteria violation – 4
- Crossover between study treatments –1
- Disallowed concomitant medication – 1
- No bone scan within 6 months of study start - 1

DEB-96-TRI-01 [Second Phase]

Safety population - Two hundred eighty-five patients were enrolled in the second phase and randomized to either triptorelin pamoate or leuprolide acetate. One patient, randomized to triptorelin pamoate, was excluded from the safety population. This patient had not received either study drug.

- **Two hundred eighty-four patients were included in the safety population, 140 patients receiving triptorelin pamoate 1-mo and 144 patients receiving leuprolide acetate.**

Intention-to-treat population - The intention-to-treat [ITT] population was defined as all patients who received either study drug and had a measurement of the primary efficacy variable, serum testosterone on day 29.

Three triptorelin pamoate 1 mo. patients were excluded, one patient due to death within the first month and two patients due to loss to follow-up.

Four leuprolide acetate patients were excluded due to death [one patient], loss to follow-up [two patients], and protocol violation [one patient].

- Two hundred seventy-seven patients were included in the ITT population, **137 patients receiving triptorelin pamoate 1-mo.** and 140 receiving leuprolide acetate. The racial distribution of the triptorelin pamoate 1-mo patients was 58.4% Caucasian, 40.9% Black/Colored and 0.7% Other.

The sponsor defined a per-protocol population [PP], excluding those patients from the ITT population who:

- Received non-permitted concomitant treatments
- Violated clinically relevant inclusion/exclusion criteria
- Did not comply with treatment
- Had no assessment before going off treatment due to loss to follow-up, refusal to continue treatment or concurrent illness.

The sponsor used the PP population in reporting efficacy outcomes in the integrated safety analysis.

Two patients receiving triptorelin pamoate were excluded from the ITT population for either violation of exclusion criteria [one patient with a low baseline serum testosterone] or out of schedule study drug administration.

Three patients receiving leuprolide were excluded from the ITT population for prior hormonal treatment for prostate cancer [two patients] or non-permitted concomitant medications [corticosteroids; one patient].

- The PP population for triptorelin pamoate 1-mo was 135 patients. The PP population for leuprolide acetate was 137 patients.

Early withdrawals from study - Of the 284 patients in the safety population, 43 patients did not complete the nine-month treatment interval.

Twenty patients of the 140 patients in the triptorelin pamoate safety population did not complete nine months of treatment.

Twenty-three patients of the 144 patients in the leuprolide acetate safety population did not complete nine months of treatment.

The reasons for withdrawal are noted in the following table:

Reasons for withdrawal from study [safety population]		
Reason	Triptorelin pamoate	Leuprolide acetate
Drug-related adverse event	1	0
Patient lost to follow-up	11	5
Insufficient therapeutic effect	1	1
Death	4	13
Protocol violation	1	3
Consent withdrawn	1	1
Other	1	0
total	**20**	**23**

The sponsor had specified that, in accounting for missing data in the assessment of efficacy, drop-outs would be counted as failures if the cause for withdrawal was a drug-related adverse event and counted as successes if the cause for withdrawal was a non-drug related event or loss to follow-up with the last testosterone value at castrate levels.

Using these criteria, of the 17 triptorelin pamoate patients who dropped out from the ITT population and had missing data, all were counted as successes in the efficacy analysis of the maintenance endpoint.

- **For the triptorelin pamoate 1-mo. patients, 120 patients remained enrolled through day 253 [month nine] of the trial. Seventeen patients of the 137 patients in the ITT population [12.4%] had withdrawn. For the leuprolide acetate patients, 123 patients remained enrolled through day 253 [month nine] of the trial. Seventeen of the 140 patients in the ITT population [12.1%] had withdrawn.**

Protocol violations were reported for 32 patients receiving triptorelin pamoate and 43 patients receiving leuprolide. The majority of the minor violations recorded for both arms were delays in obtaining a baseline bone scan until after study start. A few patients were receiving a contra-indicated drug [coumarin or corticosteroids]. The major protocol violations are noted in the following table:

Summary of major protocol violations			
Class of violation	Description of violation	Triptorelin pamoate	Leuprolide acetate
Study indications	Serum testosterone < 5 nmol/L on day 1	1	0
	No bone scan	0	1
	Prior hormonal treatment for prostate cancer	0	2
Medications	Corticosteroids [except topical]	3	5
	Medications affection metabolism of androgens	1	1
	Other androgenic medication	1	1
Study drug	Crossover between study treatments	2	1
	Out of schedule drug administration	7	6
	Total	**15**	**17**

9. Assessment of Efficacy

Overview – In response to the non-approval of this drug in 1997, the sponsor submitted a modified protocol to study an appropriate population of men with advanced prostate cancer, comparing the to-be-marketed formulation of triptorelin pamoate 1-month depot dose with leuprolide acetate 7.5 mg 1-month depot.

The final protocol included a statistical analysis plan that specified that triptorelin pamoate would be considered non-inferior to the currently-marketed leuprolide acetate if the lower bound of the two-sided, 95% confidence interval [CI] applied to the difference between the two populations for achievement of castration on day 29 was not more than – 10%.

On analysis of the performance of these two drugs, the sponsor found that the CI surrounding the difference between the two drugs was [-15.7 %, -1.4 %]. The sponsor stated that leuprolide acetate patients in this study demonstrated an unusually high achievement of castration rate, 99.3 %, compared to historical controls. This high rate was felt, by the sponsor, to accounted for the failure of triptorelin pamoate to demonstrate non-inferiority.

However, in order to address this failure to demonstrate non-inferiority, the sponsor created an integrated efficacy analysis that used a pool of population data from disparate sources, including historical data from previous leuprolide acetate studies, to attempt to demonstrate that triptorelin pamoate performance, on the achievement of castration endpoint, falls within the – 10 % lower bound.

By performing the analysis with these pooled populations, the sponsor was able to claim that the 95% two-sided confidence interval for the difference between study groups in the achievement of castration rate was –9.2%, <0.1%. Since the lower tail of this confidence interval was within 10% of the leuprolide rate, the claim of statistical non-inferiority was made.

Reviewer comment - The reviewer believes that the analysis using pooled data in the integrated efficacy analysis does not support the efficacy of this drug. However, review of the data from the "stand-alone" second phase of the DEB-96-TRI-01 study, comparing only those patients receiving triptorelin pamoate or leuprolide acetate in a randomized, prospective trial, suggests that triptorelin pamoate is clinically equivalent to leuprolide acetate in successfully achieving and maintaining castrate levels of testosterone. The sponsor's original pooled analysis and the reviewer's re-analysis are presented below.

Sponsor's integrated efficacy analysis

The sponsor combined efficacy data from the patients randomized to triptorelin pamoate 1-month in the two phases of DEB-96-TRI-01 and the two uncontrolled trials, DEB-96-TRI-02 and DEB-98-TRI-01, to produce an integrated efficacy analysis.

Studies DEB-96-TRI-02 and DEB-98-TRI-01 were small, short duration, open label, non-comparative trials of triptorelin pamoate. The first study enrolled 32 patients for a trial lasting two months. Patients received two injections of triptorelin pamoate at

28 day intervals. Data was available for assessment of the "achievement" endpoint but not the "maintenance" endpoint. Serum testosterone levels were measured on day 29, before the second dose of triptorelin pamoate, and on day 56. On day 29, 93% of patients had achieved a castrate level of testosterone [< 1.735 nmol/L] and all 32 patients had achieved or maintained castrate levels of testosterone by day 57.

The second study, DEB-98-TRI-01, enrolled 13 patients for a trial lasting 31 days. Data was available for assessment of the "achievement" endpoint but not the "maintenance" endpoint. Serum testosterone levels were obtained for each patient at time zero, at 1, 2, 3, 4, 6, 8, 12, and 24 hours on day 1, then on days 3, 4, 5, 6, 7,8, 14, 21, and 28. Serum LH levels were obtained from all patients at 2, 4, and 6 hours after each dosing of triptorelin pamoate.

On day 14, 77% of patients had achieved castrate levels of testosterone. On day 21 and day 28, all thirteen patients had testosterone levels of < 1.735 nmol/L.

Primary Efficacy Endpoint

Achievement of castration by day 29

Using the per-protocol populations from the four Debio studies, 332 patients were available for measurement of the primary efficacy variable, serum testosterone, at day 29. Of these patients, 305 had achieved castrate levels of testosterone, for a success rate of 91.9%.

The ability of leuprolide acetate to achieve castrate levels of testosterone by day 28 was reported by pooling the data from the patients in the leuprolide arm of the DEB-96-TRI-01 [second phase] study with the success rates reported in four leuprolide studies submitted to support the approval of Lupron™ [TAP] depot 7.5 mg, 22.5 mg, and 30 mg formulations.

The pooled population in the five leuprolide studies included 336 patients, 321 of whom were reported to have achieved castrate levels by day 29, a success rate of 95.5%.

A two-tailed, 95% confidence interval for the -3.6% difference between these two treatments was –9.2%, < 0.1%. The sponsor had specified that the definition of non-inferiority between the triptorelin pamoate product and leuprolide acetate was a lower bound of no more than 10% in the 95% CI constructed for the difference between the two drug products.

Based on this definition, the sponsor claimed "non-inferiority" between triptorelin pamoate and leuprolide acetate in achieving castration.

The sponsor offered no information on the results of an analysis of the ITT population for this same efficacy endpoint.

Maintenance of castration – months 2 through 9

The data used to assess the "maintenance of castration" co-primary endpoint in the triptorelin pamoate 1-month patients was obtained from patients in both DEB-96-TRI-01[first phase] and DEB-96-TRI-01[second phase]. Two hundred ninety-four patients were included in the PP population. The data for the leuprolide patients was obtained only from the per-protocol population of the DEB-96-TRI-01 [second phase] study [n=137].

Using a survival analysis methodology, the probabilities of maintenance of castration for nine months were 92.8% [two-tailed 95% CI: 88.0%, 97.7%] for triptorelin pamoate and 92.9% [two-tailed 95% CI: 88.4, 97.4%] for leuprolide acetate.

The difference between the triptorelin pamoate and leuprolide treatments was not statistically significant [p = 0.341, the two-tailed 95% CI around the difference, -6.7, 6.6]. The sponsor had specified that, for this endpoint, non-inferiority would be defined as a lower bound of the CI for the difference between treatments of no greater than – 10%.

Based on this definition, the sponsor claimed that maintenance of castration was "equivalent between the two treatments".

A similar analysis was reported for the ITT population. Data were obtained from 300 triptorelin pamoate-treated patients and 140 leuprolide acetate-treated patients. The probabilities of maintenance of castration for nine months were 92.8% [two-tailed 95% CI: 88.4%, 97.1%] for triptorelin pamoate and 90.9% [two-tailed 95% CI: 86.1%, 95.8%] for leuprolide.

The difference between the triptorelin pamoate and leuprolide treatments was not statistically significant, [p = 0.15, the two tailed 95% CI around the difference, -4.7%, 8.4%].

Reviewer comments on Efficacy assessment

The pooled analysis presented by the sponsor in the Integrated Efficacy Analysis can be criticized on several points:

- *The population evaluated was the per-protocol rather than the intention-to-treat cohort.*
- *The pooling of data for achievement of castration on day 29 from leuprolide acetate-treated patients in the second phase study and the historical results from four Lupron studies is methodologically suspect.*

- *The pooling of data for achievement of castration on day 29 from triptorelin pamoate-treated patients in the four DEB studies is methodologically suspect.*

The current view of the Division is that approval of this class of drugs for this indication should be based on demonstration of a timely achievement of castrate levels of testosterone and the reliable maintenance of these castrate levels over the course of each dosing interval. Currently approved drugs have demonstrated these characteristics over at least three dosing cycles. Generally, drugs approved for this indication have been compared with active comparators, either previously approved GnRH agonists, oral estrogen, or orchiectomy.

From a clinical perspective, the time to achievement of medical castration by GnRH agonists is less critical in the management of this patient population than the reliable maintenance of castration over months to years of testosterone suppression.

The approved indication for this class of drugs is the palliative treatment of advanced prostate cancer. The most common clinical setting for use is the long-term administration to achieve and maintain medical castration at the time when a patient shows clinical symptoms or laboratory/imaging signs of progressive metastatic disease.

Many patients are placed on this medication while they are still asymptomatic. Most will continue on the medication for several years or more. Very few patients will require rapid castration. If so, there are other treatment options that are more appropriate.

When the first GnRH agonist was being developed in the early 1980's, it was felt that patients might be at significant risk of worsening of metastatic disease due to the clinical flare at the time of first dose or on repeat dosing. This possibility is much less likely in the earlier stage patients now treated with this class of drug. Nevertheless, the absence of a significant 'acute-on-chronic' LH release and testosterone increase above castrate levels remains a desirable characteristic of a drug used for this indication and should be considered in evaluating the risk/benefit profile during the review process.

In responding to the non-approval of this drug in 1997, the sponsor submitted a protocol amendment for the second phase of the DEB-96-TRI-01 study. Treatment-naïve, advanced stage prostate cancer patients were randomized equally to either the to-be-marketed triptorelin pamoate 1-month or to leuprolide acetate one-month depot formulation. This reviewer believes that the direct comparison of both treatment group for timely achievement of castration, reliable maintenance of castration, and avoidance of a significant incidence of the 'acute-on-chronic' phenomenon is the best measure of this drug's efficacy.

The efficacy results of the patients randomized to the triptorelin pamoate arm of the first phase may be supportive of the second phase results. In addition, the small,

short-term, non-comparator studies DEB-96-TRI-02 and DEB-98-TRI-01 may offer additional support for the ability of this drug to achieve castrate levels.

Reviewer's analysis of efficacy data from DEB-96-TRI-01 [second phase]

The intention-to-treat [ITT] population was defined in the second phase study as those patients who received a dose of drug on day 0 and then had a day 29 serum testosterone level performed. This population, rather than the per-protocol [PP] population, is the most suitable for primary analysis.

One hundred forty one patients were randomized to triptorelin pamoate and 144 patients to leuprolide acetate. One triptorelin pamoate patient was excluded from the safety population, having received neither study drug. Three triptorelin pamoate patients and four leuprolide acetate patients were excluded from the ITT population, having not had a serum testosterone determination at day 29. The ITT populations for triptorelin pamoate and leuprolide acetate were 137 and 140 patients, respectively.

The demographic characteristics of both populations were reviewed and were similar for age, weight, disease duration and age at onset of disease. The stage of the prostate cancer was also similar, both populations composed of approximately 60 % stage C and 40 % stage D patients. The mean testosterone levels for the triptorelin pamoate and leuprolide acetate groups were 12.07 and 12.03 nmol/L.

Achievement of castration

Leuprolide acetate - All but one of the 140 leuprolide acetate patients had achieved castrate levels of testosterone at day 29. This achievement rate of 99.3 % excluded one patient, 06 271, whose testosterone remained above 1.735 nmol/L at all data points through day 253 [month nine] except for days 113 and 141. His values ranged from 1.8 to 5.1 nmol/L.

> *Reviewer comment - This same patient was included in a fifteen patient subset of the leuprolide acetate population that received frequent testosterone levels for the 24 hours after the dose on day 85. He was one of three patients who demonstrated an 'acute-on-chronic' testosterone flare. His baseline testosterone was 1.9 nmol/L, increasing at 2, 4, 8, 12, and 24 hours to range from 2.0 at two hours to 4.8 nmol/L at 24 hours.*
>
> *The 99.3 % castration rate is higher than the 91 %, 92 %, 94 %, and 97 % values reported for the four phase III efficacy studies used to support the registration of the leuprolide acetate depot products currently marketed. The pooled success rate for these four studies is 185 of 199 patients, or 93 %.*

Triptorelin pamoate - All but 12 of the 137 triptorelin pamoate patients had achieved castrate levels of testosterone at day 29. This achievement rate was

91.2 %.

The point estimate of the difference between the two arms, - 8.0 % has a two-sided 95% confidence interval of [–15.7 %; - 1.4 %]. This lower bound of the confidence interval exceeds the specified –10 % lower bound that the sponsor declared as the limit to define equivalence of effect.

Reviewer comment - Of the 12 triptorelin pamoate patients who failed to achieve castration on day 29, eleven of the twelve achieved castrate levels on day 57. All eleven patients remained in the study through day 253 and maintained castrate levels at all study points.

The twelfth patient [16 215] had a serum testosterone of 2.0 on day 57 and was lost to follow-up after that visit. This patient was one of five patients counted as an escape and failure in the maintenance evaluation.

Maintenance of castration

The sponsor defined success in maintenance of castration as all patients whose serum testosterone levels remained below 1.735 nmol/L at all data points from months 2 [day 57] through month nine. For those patients who dropped out or were withdrawn from the study before month nine, the sponsor specified that missing data would be handled as follows:

- Those patients who had maintained a castrate level through the last data point would be counted as a success if the withdrawal was due to non-drug related reasons.
- Those patients who had maintained a castrate level through the last data point would be counted as an escape if withdrawal was due to drug related reasons
- Those patients with missing data between two visits where castration levels were maintained would be counted as maintaining castration.

Patient escapes at day 57 - Of the 125 triptorelin pamoate patients castrate at day 29, two patients [06 207, 28 201] had escapes recorded on day 57, 9.3 and 2.5 nmol/L respectively. Both patients achieved castrate levels at day 85. Patient 28 201 remained castrate at all data points through month 9. Patient 06 207 had one other escape at month eight.

The sponsor counted these two patients, plus patient 16 215, who was not castrate at day 29 or day 57, as failures at the beginning of the maintenance period.

Of the six patients whose day 57 testosterone levels were missing, all six dropped out due to non-drug related reasons and had castrate levels of testosterone at day 29. These six patients were counted as successes.

The maintenance of castration rate at day 57 for triptorelin pamoate 1-month is 134 of 137 patients, 97.8%.

For leuprolide acetate, the day 57 maintenance rate is 136 of 140 patients, 97.1 %.

Maintenance of castration through nine months – In the triptorelin pamoate 1-month group, five patients were found to have one or more escape value between months 2 and 9.

- The "maintenance" success rate for triptorelin pamoate patients is 132 of 137 patients, 96.4 %.

In the leuprolide acetate population, 12 patients were noted to have one or more escape value between months 2 and 9. Two of these twelve patients had escape values obtained after missing their scheduled dose of leuprolide acetate one month earlier.

- The "maintenance" success rate for leuprolide acetate patients is 128 of 140 patients, 91.4 %.

Reviewer comment – The reliability of maintenance of castration can also be redefined in two other ways and the performance of triptorelin pamoate and leuprolide acetate compared:

- *If maintenance of castration is defined as no serum testosterone levels > 1.735 nmol/L through nine months in those patients who reach castrate levels at day 29, four patients of the 125 triptorelin pamoate patients castrate at day 29 had one or more escape, a 3.2 % failure to maintain rate. The castration maintenance rate for triptorelin pamoate is 121 of 125 patients, 96.8 %.*

  For leuprolide acetate, 11 of the 139 leuprolide acetate patients castrate at day 29 had one or more escape, a 7.9 % failure to maintain rate. The castration maintenance rate for leuprolide acetate is 128 of 139 patients, 92.1 %.

- *If maintenance of castration is calculated for the two study drugs through three dosing cycles, day 85, the treatment interval currently preferred for evaluation of drugs in this class for this indication, the success rate for triptorelin pamoate is 134 of 137 patients, 97.8 % and for leuprolide acetate is 133 of 140 patients, 95.0%.*

Assessment of "acute-on-chronic" flare phenomenon

Rather than measure serum testosterone levels during the first twenty-four hours after repeat dosing with triptorelin pamoate and leuprolide acetate, the sponsor chose to measure LH levels. The sponsor specified that a significant flare phenomenon would

be defined by an LH value of > 1.0 IU/L at the 2 hour timepoint after dosing on days 85 and 169.

Reviewer comment - Although the sponsor submitted no rationale for the choice of two hours post-dose as the optimal timepoint for measuring LH levels, review of data from study DEB-96-TRI-02 suggests that, in the majority of those patients, the 2 hour post-dose LH level did represent the peak value during the six hour sampling interval.

Using this definition, the triptorelin pamoate patients at day 85 [n=126] demonstrated a significant flare in 2 of 126 patients, a failure rate of 1.6 %. At day 169, the failure rate was 2 of 123 evaluable patients, 1.6 %.

The leuprolide acetate patients at day 85 [n= 130] demonstrated flare in 8 of 130 patients, a failure rate of 6.2 %. The failure rate at day 169 was 8 of 122 evaluable patients, 6.6 %.

Reviewer comment – The sponsor did not attempt to link these LH levels to either testosterone levels or clinical signs of flare. However, in a subset of approximately 10 % of the study population, serum testosterone was sampled frequently during the 24 hours after administration of GnRH agonist on day 85. Serum testosterone was found to be elevated above castrate levels at one or more sampling points in none of 14 triptorelin pamoate patients and in three of 15 leuprolide acetate patients. Summaries of two of the leuprolide patients demonstrate the potential clinical significance of the flare and escape associated with repeat dosing:

- *Patient 01 202 achieved castrate levels of testosterone on day 29 [0.2 nmol/L] and remained castrate at day 57 and at time zero on day 85 [0.9 nmol/L]. The LH level drawn at time zero was elevated at 1.9 IU/L and increased to 5.5 IU/L at 2 hours. His serum testosterone escaped above castrate levels to the range of 2.3-4.4 nmol/L at sampling points from 2-24 hours. This patient later was noted to escape castration on monthly monitoring at days 141 and 169 and was counted as one of the leuprolide acetate patients who failed to maintain castration.*

- *Patient 01 207 achieved castrate levels of testosterone on day 29 [0.7 nmol/L] but escaped castration by day 57 [12.7 nmol/L] and day 85 [10.2 nmol/L]. The LH level drawn at time zero, day 85 was elevated at 3.2 IU/L and increased to 10.2 IU/L at 2 hours. His serum testosterone levels on day 85 ranged from 10.8 to 13.8 nmol/L on sampling from 2-24 hours. On monthly monitoring his testosterone was 0.2 nmol/L on day 113 but had again escaped above castrate levels [7.5 nmol/L] on day 141. The patient died before his next follow-up exam. The cause of death was reported as pulmonary embolism.*

The response across both treatment arms suggests that each drug treatment was similar in this outcome. The two-sided, 95% confidence interval for the difference between groups at day 85 and day 169 surrounds zero, suggesting statistical

equivalence. From a clinical perspective, the rate of flare is acceptably low for triptorelin pamoate-treated patients and is similar to the rate reported for other approved GnRH agonists used for this same clinical condition.

Supportive efficacy data – DEB-96-TRI-01 [first phase]

Achievement of castration

One hundred sixty-four patients were included in the ITT population receiving the triptorelin pamoate 1-mo. formulation.

One hundred fifty-two patients [92.7 %] had achieved castrate levels of testosterone by day 29.

This result is similar to the 91.7 % "achievement" rate reported for the ITT population of triptorelin pamoate-treated patients in the second phase of the trial.

Maintenance of castration

Of the 164 patients included in the ITT population, six patients had missing data on day 57. The sponsor defined success in maintenance of castration as all patients whose serum testosterone levels remained below 1.735 nmol/L at all data points from months 2 [day 57] through month nine. For those patients who dropped out or were withdrawn from the study before month nine, the sponsor specified that missing data would be handled as follows:

- Those patients who had maintained a castrate level through the last data point would be counted as a success if the withdrawal was due to non-drug related reasons.
- Those patients who had maintained a castrate level through the last data point would be counted as an escape if withdrawal was due to drug related reasons.
- Those patients with missing data between two visits where castration levels were maintained would be counted as maintaining castration.

Using these criteria, all six patients with missing data were counted as "successes" at day 57. One hundred sixty-two of 164 patients [98.8%] were castrate at month 2, the beginning of the "maintenance" treatment interval.

One hundred thirty-five of the 164 patients in the ITT population completed nine months of maintenance. Of the twenty patients who dropped out and had missing data, all twenty were counted as "successes" based on the pre-specified criteria noted above.

The maintenance of castration rate for the ITT population in the first phase of DEB-96-TRI-01 was 155 of 164 patients, 94.2%.

This result is similar to the 96.4% "maintenance of castration" rate reported for the ITT population of triptorelin pamoate-treated patients in the second phase of the trial.

Assessment of "acute-on-chronic" flare phenomenon

Evaluation for flare of LH at 2 hours after dosing with triptorelin pamoate 1 mo. dosing on days 85 and 169 was performed on 156 patients on day 85 and 149 patients on day 169.

The proportion on triptorelin pamoate-treated patients showing an increase in serum LH < 1.0 IU/L was 152 of 156 patients [97.4%] at day 85 and 146 of 149 patients [98.0%] at day 169.

These results are similar to the 98.4% "avoidance of flare" rate reported for the ITT population of triptorelin pamoate-treated patients in the second phase of the trial.

Other efficacy endpoints

The sponsor submitted outcomes for three secondary variables – PSA levels, bone pain, and quality of life. This information has been reviewed.

Reviewer comment - The data from measurement of these secondary endpoints is exploratory in nature and will not contribute to an assessment of efficacy in consideration of approval of this drug.

10. Assessment of Safety

The primary safety data in the present submission are from the large, two-phase DEB-96-TRI-01 trial and two small uncontrolled trials, DEB-96-TRI-02 and DEB-98-TRI-01. The total number of patients exposed to triptorelin pamoate in the safety database was 357 patients. In addition, the sponsor submitted safety data on two comparator drugs, 174 patients receiving the 3-month formulation of triptorelin pamoate in the first phase of DEB-96-TRI-01 and 144 patients receiving leuprolide acetate 1-month depot 7.5 mg in the second phase of DEB-96-TRI-01.

At the time of the original filing of NDA 20 715 June 24, 1996 the sponsor submitted safety data from four clinical trials performed with triptorelin acetate, a compound not identical to the to-be-marketed triptorelin pamoate formulation under NDA review. Those four trials are included in the current submission as supportive evidence of safety of triptorelin.

Duration of exposure - The 312 patients receiving triptorelin pamoate in the DEB-96-TRI-01 trial were exposed to up to nine monthly doses of the study medication. The 32 patients in the DEB-96-TRI-02 trial all received two monthly doses of the medication. All thirteen patients in the DEB-98-TRI-01 trial received a single depot monthly dose of triptorelin pamoate. Of the 357 triptorelin pamoate-treated patients in the pooled population, 49 patients [13.7%] discontinued early.

Disposition of patients -The safety population of 357 patients exposed to triptorelin pamoate represents all but two patients enrolled in the four trials. One patient from each phase of the DEB-96-TRI-01 trial was excluded, having withdrawn without receiving any study drug.

The safety data for assessment of adverse events was pooled from both phases of the DEB-96-TRI-01 and DEB-98-TRI-01 studies. Data from the 32 patients in the DEB-96-TRI-02 study was not included, and was reported separately since the methodology for collecting adverse event reports differed for this trial from that of the other three trials. The integrated summary of safety presents a comparison of the adverse event results from the pooled 325 patients receiving triptorelin pamoate with the 144 patients from DEB-96-TRI-01 [second phase] who received leuprolide acetate.

Serious Adverse Events and Deaths

Serious adverse events [SAE], SAEs leading to withdrawal from study, and all deaths are tabulated in the following table.

Overview of Deaths and SAEs in triptorelin pamoate Treated patients by Study: pooled safety population
DEB-96-TRI-01, DEB-96-TRI-02, DEB-98-TRI-01

	Deaths	Withdrawal due to SAE	SAEs not leading to withdrawal
DEB-96-TRI-01[First Phase]	13	1	25
DEB-96-TRI-01[Second Phase]	6	1	22
DEB-96-TRI-02	3	1	6
DEB-98-TRI-01	1	0	1

Withdrawals due to serious adverse events

The three patients who discontinued treatment, after randomization, due to a serious adverse event included:

Patient 12002 – This man was noted to have an inguinal hernia within a few weeks of his first dose of triptorelin pamoate. He chose to have an inguinal hernia repair and elective bilateral orchiectomy at the same time. The patient was withdrawn from the study after the orchiectomy.

Patient 27206 - The patient began treatment with triptorelin pamoate May 1998 and developed asthenia September 1998. He was withdrawn from the study.

Patient 6 – The patient was noted to have three SAEs reported concurrently – chest infection, diarrhea, and pulmonary infection—occurring about two weeks after the initial dose of triptorelin pamoate.

Serious adverse events not leading to withdrawal

Study DEB-96-TRI-01[First Phase] – Of the 172 patients in the safety population, 25 patients had 26 mentions of an SAE. Twenty-three of these AEs were believed by the sponsor to be not related to the study drug. Three events were believed to have an "unlikely relationship" to the study drug.

Study DEB-96-TRI-01[Second Phase] - Of the 140 patients in the safety population, 22 patients had 23 mentions of an SAE. Twenty-two of these adverse events were believed by the sponsor to be not related to the study drug. The one AE felt to have an unlikely relationship to the study drug was patient 25215 who began treatment with triptorelin pamoate May 1998 and was noted to have anemia three months later.

Study DEB-96-TRI-02 - Six serious adverse events were recorded for 4 of the 32 patients enrolled in this study. Five events were believed by the sponsor to be not related to the study drug. One event, a chest infection in patient 20, was felt to be unlikely to be related to the study drug.

Study DEB-98-TRI-01 – Of the 13 patients enrolled in this trial, one patient was noted to have uncontrolled hypertension. The sponsor believed that this event was not related to the study drug.

Serious allergic adverse events - world-wide post-marketing experience

The sponsor provided the results of a review of periodic safety update reports for immunogenic adverse events reported from 1987 through October 1997. During this interval, approximately [redacted] vials of triptorelin were sold. Seven reports of angioedema, 3 reports of anaphylactic shock, and 48 individual reports of rash, urticaria, eczema, edema, pruritus, and allergy were noted.

Reviewer comment - This reviewer does not believe that any of the serious adverse events reported and reviewed above are related to the effects of the study drug. The reports of the rare occurrences of allergic adverse events, gathered from the spontaneous post-marketing reporting over a ten-year interval, suggest a low incidence of allergic reactions, with most events self-limited and reversible with treatment.

Deaths

Overview – Twenty-three deaths were reported from the safety population of 357 triptorelin pamoate-treated patients in the pooled population. The sponsor reported that 15 deaths were noted in the safety population of the 144 leuprolide-treated patients. Most of the deaths reported in either treated populations were ascribed to disease progression of the patient's advanced stage adenocarcinoma of the prostate or due to cardiovascular events such as myocardial infarction or congestive heart failure.

DEB-96-TRI-01[first phase] – Thirteen deaths were reported for the 172 triptorelin pamoate-treated patients included in the safety population. Five patients died of prostate cancer and five patients had cardiac related deaths due to myocardial infarction, ischemic heart disease, or congestive heart failure. The three remaining deaths were ascribed to COPD, aneurysm, and acute pyelonephritis.

Disease Progression deaths

Patient 03002 – disease progression – The patient was diagnosed with stage T4 Nx M1 carcinoma of the prostate in July 1996. Bone scan showed metastases at that time. The first dose of study drug was received in February 1997. Bone pain was reported as increased in April 1997 and a bone scan at that time showed progression of the skeletal metastases. The patient required hospitalization in May 1997 for pain control. He was admitted to hospice care in August 1997 and died 8/22/97 of disease progression. No post-mortem was performed.

Patient 03005 – disease progression – The patient was diagnosed with well differentiated carcinoma of the prostate in August 1992. A bone scan February 1997 showed metastases, the tumor staged as T3 Nx M1. He received his first dose of study drug in February 1997. In April 1997 the patient was reported to have shortness of breath, confusion, hypertension, and nausea. His symptoms were managed medically. In May 1997 his PSA was reported as 260 g/L compared to a baseline level of 151 g/L three months earlier. He died on 6/03/97 with his death ascribed to disease progression.

Patient 03021 – disease progression – The patient was diagnosed with stage T4 Nx M1 prostate cancer in May 1997. Bone scan showed metastatic disease. He

received his first dose of study drug in May 1997. In June1997, he was admitted to the hospital with dyspnea. The diagnosis of respiratory distress due to lung metastases and pleural effusion was made. The patient died 6/30/97 with death ascribed to disease progression. No post-mortem was performed.

Patient 03036 – disease progression – The patient was diagnosed with stage T4 N2 M0 carcinoma of the prostate in July 1997. Metastases to several pelvic lymph nodes was noted at the time of radical prostatectomy. He received his first dose of study drug August 1997. A pelvic lymphocele was identified and drained under ultrasound guidance November 1997. The patient complained of severe pelvic pain January 1998 and received a course of radiotherapy for pain relief. He died 3/23/98 at home with death ascribed to disease progression. No post mortem was performed.

Patient 16024 – disease progression – The patient was diagnosed with stage T4 Nx M1 carcinoma of the prostate, the bone scan showing wide-spread bone metastases, October 1997. He received his first dose of study drug 10/15/97. In March 1998 he began to complain of pain in his left hip. X-ray of the hip did not confirm fracture or metastatic disease. He continued to complain of bone pain and weakness. He died at home 06/01/98 with death ascribed to disease progression.

Reviewer comment - The disease progression of the carcinoma of the prostate that led to these patient deaths was not due to failure of the study drug to suppress serum testosterone. In all patients, the last serum testosterone drawn prior to death was < 1.735 nmol/L.

Cardio-pulmonary related deaths

Patient 03019 – Myocardial infarction - The patient was diagnosed with a well-differentiated carcinoma of the prostate. Bone scan April 1997 showed multiple skeletal metastases, stage T4 Nx M1. He received his first dose of study drug May 1997. The patient presented to his physician 7/3/97 with complaints of discomfort in the chest for one day. He collapsed and could not be resuscitated. His death was ascribed to a cardiac arrest secondary to myocardial infarction. No post-mortem was performed.

Patient 03038 – Cardiac arrest – The patient was diagnosed with stage T4 Nx Mx carcinoma of the prostate July 1997. He received his first dose of study drug August 1997. His medical history included COPD, ischemic heart disease, and hypertension. On 10/11/97 the patient collapsed and died on the street. The death was ascribed to cardiac arrest due to known underlying ischemic heart disease. No post-mortem was performed.

Patient 04002 – Ischemic heart disease - The patient was diagnosed with stage T3 Nx M0 carcinoma of the prostate January 1997. He received his first dose of study drug April 1997. His medical history included hypertension, ischemic heart disease, COPD, diabetes, and congestive cardiac failure. In August 1997 the patient was admitted to the hospital with left-sided chest pain and dyspnea. His diagnosis was of unstable angina, congestive heart failure, and bilateral pleural effusions. He was treated medically, improved and was discharged on the sixth hospital day. He died suddenly at home eight days later. No post-mortem was performed.

Patient 04016 – COPD – The patient was diagnosed with stage T2b Nx M1 carcinoma of the prostate September 1997 with bone scan demonstrating widespread skeletal metastases. He received his first dose of study drug October 1997. His medical history included pneumoconiosis and COPD. From November 1997 to June 1998 he was treated with medications for increasing bone pain. A bone scan June 1998 was reported to show 'no improvement' from that of October 1997. He was placed on Eulexin 750 mg daily in August 1998. He was reported to have an 'acute exacerbation of his COPD' on 9/25/98 and died the same day. The reporter ascribed the death to an acute cardiac arrest. No post-mortem was performed.

Patient 09005 – Congestive heart failure – The patient was diagnosed with stage T3 N0 M0 carcinoma of the prostate February 1997. Bone scan showed no metastases. He received his first dose of study drug February 1997. His medical history included ischemic heart disease with previous myocardial infarction and CABG, and mitral valve incompetence. He had a past history of resection of a superficial bladder carcinoma in 1990. He was evaluated for hematuria June 1997 and found to have a 'stage II, non-infiltrating transitional bladder carcinoma.' The patient was hospitalized 8/18/97 with dyspnea and hypotension and diagnosed with congestive heart failure. He underwent unsuccessful left heart catheterization, developed 'hemodynamic collapse due to profuse bleeding from the lung' and died on 8/21/97. No post-mortem exam was performed.

Patient 09007 – Myocardial infarction – The patient was diagnosed with stage T3 N0 M0 carcinoma of the prostate March 1994. A bone scan March 1997 showed no metastases. He received his first dose of study drug March 1997. The patient's medical history included hypertension and arthritis. On 04/23/97 the patient was hospitalized with severe chest pain and diagnosed with a 'massive myocardial infarction'. He died the same day. No post-mortem was performed.

Other deaths

Patient 16007 – Acute pyelonephritis – The patient was diagnosed with stage T3 Nx M0 carcinoma of the prostate May 1997. He received his first dose of study

drug May 1997. His active medical problems included type II diabetes and hypertension. He was hospitalized September 1997 with a diagnosis of acute diabetic ketoacidosis and acute renal failure secondary to acute pyelonephritis. He was treated with antibiotics, intravenous fluids, and parenteral nutrition. He died 9/6/97, the death ascribed to pyelonephritis.

Patient 17002 – Aneurysm – The patient was diagnosed with stage T2 N0 M x, well-differentiated carcinoma of the prostate in May 1997. Bone scan was negative for metastasis. He received his first dose of study drug September 1997. In October 1997 the patient was hospitalized with severe abdominal pain and an abdominal aortic aneurysm diagnosed. The patient died on 10/31/97.

Reviewer comment - This reviewer believes that the deaths reported and reviewed in DEB-96-TRI-01 [first phase] are not related to the effects of the study drug.

DEB-96-TRI-01[second phase] – Six deaths were reported for the 140 triptorelin pamoate-treated patients included in the safety population. Two patients died of progressive prostate cancer. A third patient was recorded as dying from "general demise". The three remaining deaths were ascribed to perforated peptic ulcer, chronic renal failure, and metastatic liver disease.

Disease progression deaths

Patient 01206 – disease progression - The patient was diagnosed with stage T3 Nx M1 carcinoma of the prostate February 1998. Bone scan March 1998 showed widespread metastasis. He received his first dose of study drug 03/30/98. The investigator was informed by the patient's family that he died in his sleep 04/11/98. No post-mortem was performed. The investigator ascribed the death to disease progression.

Patient 07209 – disease progression – The patient was diagnosed with stage T4 Nx M1 carcinoma of the prostate January 1998. Bones scan showed diffuse skeletal metastasis. He received his first dose of study drug January 1998. He was hospitalized October 1998 with severe pain in the back and shoulders. X-rays of his pelvis and chest showed diffuse metastasis. He was treated medically and died 10/18/98. No post-mortem was performed.

Reviewer comment - The disease progression of the carcinoma of the prostate that led to these patient deaths was not due to failure of the study drug to suppress serum testosterone.

Other deaths

Patient 04211 – perforated peptic ulcer – The patient was diagnosed with stage T3 Nx Mx carcinoma of the prostate April 1998. He had his first dose of study drug May 1998. The patient was hospitalized with hematemesis 06/30/98. Gastroscopy demonstrated erosive gastritis. The patient's condition worsened on 07/04/98 and he died the following day. His death was ascribed to a perforated peptic ulcer. No post-mortem was performed.

Patient 07202 – chronic renal failure – The patient was diagnosed with stage T4 Nx M1 carcinoma of the prostate January 1998. Bone scan demonstrated extensive skeletal metastasis. He received his first dose of study drug January 1998. His last dose of study drug was received 02/17/98. The patient was lost to follow-up for two months and then hospitalized April 1998 with dyspnea and dependent edema. A diagnosis of hypertension, chronic cardiac and renal failure was made. The patient was treated medically, showed improvement and with discharged 05/12/98. He died at home 05/27/98 with death ascribed to respiratory failure. No post-mortem was performed.

Patient 21209 – "general demise" – The patient was diagnosed with stage T4 Nx Mx carcinoma of the prostate May 1998. He received his first dose of study drug May 1998. His last dose of study drug was received 01/14/99. His clinical course was one of progressive weakness. When evaluated in a nursing home January 1999 he was noted to have mild elevation of hepatocellular enzymes. An abdominal scan did not confirm liver metastases. The patient died 01/15/99 with his death ascribed to "general demise". No post-mortem was performed.

Patient 28214 – metastatic liver disease – The patient was diagnosed with stage T3 Nx M1 carcinoma of the prostate April 1998. Bone scan showed multiple metastases. He received his first dose of study drug April 1998. His last dose of study drug was 06/25/98. The patient developed acute jaundice 07/01/98, felt to be obstructive in character, based on liver function tests. He died on 07/04/98, with his death ascribed to hepatic metastasis. No post-mortem was performed.

DEB-96-TRI-02 - Three deaths were reported for the 32 triptorelin-treated patients in this trial. One death each was ascribed to renal insufficiency, pneumonia, and "died in sleep".

Patient 09 received his two monthly doses of study medication on 11/06/96 and 12/04/96. He was reported to have died in his sleep 01/12/97.

Patient 11 received his two monthly doses of study medication on 11/06/96 and 01/02/97. He was hospitalized with pneumonia 03/08/97 and died on 03/14/97.

Patient 22 received a single dose of study medication on 12/02/96. He died on 12/04/96 with death ascribed to "vomiting and nausea leading to dehydration and death".

DEB-98-TRI-01 – One death was reported for the 13 patients receiving a single dose of triptorelin pamoate in this trial. The death was reported as due to renal failure.

Patient 06 – The patient was diagnosed with stage T4 Nx M1 carcinoma of the prostate with bone scan showing metastases May 1998. He received his single dose of study drug 05/19/98. The patient was noted to be in urinary retention and required an indwelling catheter, placed 05/04/98. At that time, his creatinine was in the normal range. The catheter was removed 07/14/98. On 07/18/98 the patient was hospitalized with urinary retention. His creatinine was elevated to a level over five times the upper limits of normal range. He was acidotic, hypoglycemic, and hypotensive. The patient died on the day of admission.

Reviewer comment – This reviewer believes that the deaths reported and reviewed in DEB-96-TRI-01 [second phase], DEB-96-TRI-02, and DEB-98-TRI-01 are not related to the effects of the study drug.

All Adverse Events

Three hundred and three of the 325 triptorelin pamoate patients [93.2%] reported one or more AE compared with 135 of 144 patients [93.8%] receiving leuprolide acetate. There were no statistically significant differences between the triptorelin pamoate or leuprolide acetate patients for over-all AEs or across any of the sub-categories.

The sponsor also presents a comparison of the same populations for AEs reported by 5% or more patients. The most common AEs were hot flushes, [60.6%; 53.5% for triptorelin pamoate and leuprolide patients] and skeletal pain [20.9%; 14.6%]. Those AEs occurring in > 10 % of patients are included in the following table.

Adverse Event	Treatment groups				
	Triptorelin pamoate		Leuprolide acetate		p-value
	N	%	N	%	
Hot flushes	197	60.6	77	53.5	0.156
Skeletal pain	68	20.9	21	14.6	0.126
Viral infection	57	17.5	16	11.1	0.097
Headache	54	16.6	22	15.3	0.787
Constipation	46	14.2	19	13.2	0.885
Pain	41	12.6	9	6.3	0.050
Hypertension	40	12.3	19	13.2	0.765
Back pain	38	11.7	15	10.4	0.754
Arthralgia	38	11.7	16	11.1	1.000
Urinary tract infection	33	10.2	10	6.9	0.302

The sponsor states that, with the exception of the hot flushes, most of the AEs reported were considered to be not related to the study drug, triptorelin pamoate. Of the 325 patients who received triptorelin pamoate, 95 patients [29.2%] reported that at least one AE was "severe" and 273 patients rated their AE as "mild". The corresponding data from the 144 patients receiving leuprolide acetate was 49 patients [34.0%] rating their AE as "severe" and 118 patients [81.9%] reporting a "mild" AE. For the 197 triptorelin pamoate patients reporting hot flushes, 13 patients rated the symptom as severe. For the 77 leuprolide acetate patients, 3 patients rated the symptom as severe.

Reviewer comment – This reviewer believes that the adverse event profile for this drug is similar to that seen with other currently marketed, synthetic GnRH agonists approved for this indication. The most commonly reported adverse event, hot flushes, is an expected pharmacological effect of the drug.

Laboratory Abnormalities

Overview- Hematology and blood chemistry values were obtained at baseline screening, on days 1, 85, 169, and 253 for patients in both phases of study DEB96-TRI-01. For patients in study DEB-96-TRI-02, these measurements were done at baseline and on day 56. For patients in study DEB-98-TRI-01, the measurements were done at baseline and on day 31.

Hematology measures included hemoglobin, WBC count, and platelet count. Blood chemistries included blood urea nitrogen, creatinine, total bilirubin, alkaline phosphatase, SGPT/ALT, SGOT/AST, potassium, and sodium.

A laboratory value was identified as an adverse event if one or more determinations were noted to be higher or lower than the normal range on any determination after the date of the first dose of study drug. Patients with multiple abnormal occurrences for a given test were counted only once. No record was made of the degree of deviation from the normal range.

The safety population for patients exposed to triptorelin pamoate included the pooled population of 357 patients enrolled in the four studies. Comparison was made to the abnormalities reported in the population of patients [n=144] exposed to leuprolide acetate in the second phase of DEB-96-TRI-01. Most of the triptorelin pamoate patients had hemoglobin, WBC count, ALT, AST, and creatinine determinations. Three hundred twenty two patients had urea, bilirubin, and alkaline phosphatase determination. Thirty-two patients had platelet counts, potassium, and sodium determinations. All 144 leuprolide-treated patients had all laboratory tests except for platelet count, sodium, and potassium. Three leuprolide-treated patients had platelet counts measured. No leuprolide-treated patient had sodium or potassium obtained.

Laboratory results were presented as tabular summary data. No statistical analysis was performed. Review of the laboratory results demonstrated no clinically important

differences in any measure from baseline to study termination for mean values across study drugs. Mean values for hepatic, renal, and hematological function were not affected.

Vital signs and weight were reported as mean changes over time. These results demonstrated no clinically important changes.

Local reaction to the study drug at the injection site was reported in both populations at days 1, 85, and 169. Redness and induration were not reported in either treatment group. Swelling, bruising, or pain were noted by 0.7 - 4.1 % of patients at any of the three assessment points. Pain was noted in slightly more triptorelin pamoate patients than in the leuprolide acetate group [4.1% versus 1.6% on day 169].

11. Overall Assessment of Safety and Efficacy

The sponsor has submitted evidence that triptorelin pamoate is effective in achieving and maintaining medical castration in a population of patients with advanced prostate cancer. The achievement of castration occurs within a clinically meaningful time and is maintained, without escape from castrate levels, in a high proportion of patients over nine treatment cycles. The performance of this drug is clinically similar to the active comparator drug, leuprolide acetate 7.5 mg depot. There is data to support the statistical non-inferiority of triptorelin pamoate compared to leuprolide acetate in maintaining castrate levels of testosterone. There is data to support the statistical non-inferiority of triptorelin pamoate in avoidance of an "acute-on-chronic" flare phenomenon compared to leuprolide acetate. When compared to leuprolide acetate, triptorelin pamoate was not shown to be non-inferior in achievement of castration on study day 29 by the pre-specified criteria in the study protocol. However, this statistical finding was based on a rate of achievement of castration in the leuprolide acetate arm [99.3 %] that is well above the historical rates found for leuprolide acetate in previous registration studies.

Furthermore, when the data from the triptorelin pamoate patients who failed to reach castrate levels on day 29 are reviewed, all patients except one are castrate by day 59 and all of these patients maintain castration, without escape, on monthly monitoring for nine treatment cycles. This reviewer believes that the modest differences between the two study groups in achieving castration is not of clinical significance as this class of drugs is used in clinical practice.

The safety of triptorelin pamoate 3.75 mg depot dose has been satisfactorily demonstrated in a population of over 350 patients with prostate cancer, treated for up to nine months. All death narratives were examined, and this reviewer believes that none of the deaths are attributable to the effects of the triptorelin pamoate. Although some patients who died had disease progression of their prostate cancer, in none of these patients was there evidence that the castration was unsuccessful and thereby contributed to the death. The serious adverse events reported with triptorelin pamoate were similar in type and rate to those seen with the active comparator, leuprolide

acetate. There was no evidence of clinically significant hypersensitivity, hepatic, cardiac, or renal toxicity over nine months of exposure. The most commonly reported adverse events were generally attributable to the physiological effects of the GnRH agonist drug.

12. Labeling Issues

The sponsor-proposed label has been reviewed and modifications have been returned to the sponsor for comment. Changes suggested by this reviewer include:

- Elimination of direct comparison between triptorelin pamoate and leuprolide acetate for efficacy. The efficacy results of the second phase of trial DEB-96-TRI-01 are best presented as "stand alone" results reporting the study population, the primary endpoints of achievement and maintenance of castration, and the avoidance of flare.

- Elimination of direct comparison between triptorelin pamoate and leuprolide acetate for adverse events.

13. Recommendations of Medical Reviewer

The reviewer concludes that TRELSTAR® Depot is safe and effective for the palliative treatment of adenocarcinoma of the prostate in patients for whom medical castration is indicated. The reviewer recommends that TRELSTAR® Depot be approved for the indication noted above.

/s/ _MND 5/15/2000

Norman S. Marks, M.D., Medical Officer
Division of Reproductive and Urological Drug Products
HFD-580
CC: Daniel A. Shames, M.D.
Marianne Mann, M.D.
Jeanine Best, R.N.
Division File
NDA 20 715

Concur 5/18/00 MD
TL, urology
see 2° Review

Duros

NDA 20-715
Date NDA Submitted: June 24, 1996
Date NDA received: June 26, 1996
Date assigned: July 3, 1996
Review completed: May 9, 1997 JUN 27 1997
Revisions completed: June 9, 1997

Medical Officer Review

Sponsor: Debio R. P.
Case Postale
Route du Levant 146
Ch-1920 Martigny
Switzerland

Drug: **Generic:** triptorelin pamoate
Trade: Decapeptyl Depot
Chemical: Pyr-His-Trp-Ser-Tyr-D-Trp-Leu-Arg-Pro-Gly-NH_2, pamoate salt

Route: Intramuscular (I.M.)

Dosage Form: Depot suspension

Strength: 3.75 mg.

Proposed indication: Palliative treatment of advanced prostate cancer

Related INDs: [redacted] (June 11, 1986 - Decapeptyl Depot 3.75 mg. [redacted]

Related NDAs: 19-010 (leuprolide acetate, daily injection 1.0mg. approved 4/9/85)
19-732 (leuprolide acetate, Monthly Depot injection 7.50 mg. approved12/26/89)
20-517 (leuprolide acetate, 3-Month Depot injection 22.5 mg. approved 12/22/95)
19-726 (goserelin acetate, Monthly Implant injection 3.6 mg. approved 12/29/89)
20-578 (goserelin acetate, 3-Month Implant injection 10.8 mg. approved 1/11/96)

Related documents: Minor amendments received: 1/21/96, 1/23/97/, 2/7/97, 3/19/97
Minutes of Meetings: 1/16/94, 6/16/94 (Pre- NDA), 1/18/95 (Pre-NDA), 6/30/95 (Pre-NDA), 7/25/96 (Filing meeting), 2/4/97 (status meeting).
Minutes of teleconference: 1/17/
Memorandum from DSI: 3/13/97

Table of Contents for NDA 20-715
Medical Officer Review

1. Resume

This 143 volume submission from Debio R.P. contains three "core" studies in support of the indication of Decapeptyl Depot for palliation of patients with advanced prostate cancer. A total of 265 patients were enrolled in these parallel, randomized, active controlled trials. The trials compared the ability of Decapeptyl and surgical orchiectomy to induce a castrate level of testosterone (T) in patients with advanced prostate cancer and thus induce clinical palliation. The trials were carried out in England, Belgium and France between 1983 and 1989.

In each of these three studies, there were significant deficiencies in trial design, conduct, and data analysis. The sponsor's analysis of the primary efficacy variable (the ability to induce castrate levels of T in patients with advanced prostate cancer and maintain them) did not support the claim that Decapeptyl is effective for this indication. Due to inadequate and missing data no definite conclusions about the safety of Decapeptyl can be reached.

Because of these deficiencies, the Division of Reproductive and Urologic Drug Products (hereafter referred to as the Division) finds that Decapeptyl Depot is not approvable for the indication of palliative treatment of advanced prostate cancer. The application does not support the efficacy or safety of this drug.

2. Background

2.1 Regulatory History: Lederle Laboratories submitted IND [redacted] on June 11, 1986 for Decapeptyl Depot 3.75 mg (triptorelin pamoate) [redacted] Organon became the sponsor on July 20, 1987. Multiple communications and meetings occurred to discuss development for the indication [redacted] prostate cancer treatment with Organon until June 1994 when Debio became the sponsor.

During a meeting on June 16, 1994, Debio requested that Decapeptyl be approved on the basis that it is structurally similar to two approved drugs indicated for the treatment of advanced prostate cancer, leuprolide and goserelin. This request was denied. Debio then held discussions with the DMEDP regarding the suitability of three completed European trials comparing Decapeptyl with orchiectomy for the treatment of advanced prostate cancer.

Discussions and correspondence between Debio, DMEDP and DRUDP were held until the NDA was submitted in June 1996. During these discussions Debio was advised that the endpoint for the trial should be lowering of testosterone to castrate levels and that clinical improvement and mortality should be secondary endpoints. This strategy would be consistent with the approval requirements for other GnRH agonists for prostate cancer. The trials submitted by Debio were originally designed with clinical endpoints as the primary variables. The sponsor was told that the data from these trials would be acceptable if the data could be validated (1/18/95). The sponsor was told that a meta-