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## APPROVAL PACKAGE FOR:

## APPLICATION NUMBER
## 20-715

# Pharmacology Review(s)

NDA 20-715

6/15/00

JUN 15 2000

Pharmacology Team Leader Memo

The effect of triptorelin on organogenesis was examined in mice and rats. Normally the species of choice are the rat and rabbit. The mouse was chosen instead of the rabbit because of the extreme sensitivity of the rabbit to the embryolethality of GnRH agonists. The first agonist, leuprolide, was tested for teratology in rabbits and the highest dose that allowed for fetal survival was only 1/3 the human dose. It was felt at the time that the mouse, which tolerates higher doses, would allow for a more rigorous test of the teratogenic effects of these drugs.

1st 6/15

Alex Jordan, PhD

Original NDA 20-715
HFD-580
AJordan

JUN 1 - 2000

# Memorandum

Date: 14 June 2000

From: David E. Morse, Ph.D. /S/
Asc. Director (Pharm./Tox.), Office of Drug Evaluation III

To: Florence Houn, M.D.
Director, Office of Drug Evaluation III

Cc: Susan Allen, M.D., Dir., HFD-580
Alex Jordan, Ph.D., TL Pharm./Tox., HFD-580

Subject: NDA 20-715
TRELSTAR® Depot Injection
Triptorelin pamoate for depot suspension
Review of Pharm./Tox. Sections of NDA 20-715 Action Package

## I. Materials Included in Review

1. Pharm./Tox. Review of NDA 20-715, 21 Oct. 1996, written by Krishan L. Raheja, DVM, Ph.D.
2. Pharm./Tox. TL Memorandum for NDA 20-715, 18 May 2000, written by Alex Jordan, Ph.D.
3. NDA 20-715 Approval Package (16 June 2000), with draft product labeling.

Related Product Labels:

4. LUPRON® (leuprolide) Depot and Injection
5. SYNAREL® (nafarelin acetate) Nasal Solution
6. ZOLADEX® (goserelin acetate) Implant

## II. Comments and Conclusions

1. The Pharmacology review of NDA 20-715 contains a summary listing of toxicology studies conducted with triptorelan, and a listing of the sites within other submissions where these studies may be located. However, neither the individual study reports nor an integrated summary of the study findings are included in the present review/package. The listing of non-clinical studies (up to six months duration in rat, dog and cebus monkey, and carcinogenicity studies in mice and rats) conducted with triptorelin suggests that an adequate toxicological assessment of the compound may have been performed for approval of the requested indication (palliative treatment of advanced prostate cancer). However, the omission of the study reviews (and/or integrated data summaries) from the NDA Review limits the final evaluation of the NDA Action Package to the format and content of the proposed product labeling. It is suggested that, if at some future date, the product is submitted for approval of an additional indication, the Pharmacology Review be revised to include integrated summaries of the major findings from the toxicological assessment of triptorelin and to include the individual study reviews.

2. Studies of the effects of potential human pharmaceutical agents on organogenesis are generally conducted in two species, most frequently including one rodent and one non-

rodent species. According to the NDA review for triptorelin, testing for this compound was conducted in two rodent species (mouse and rat) and did not include a non-rodent species. Therefore, it is suggested that: a) a discussion of the adequacy of the rodent only testing should be included in the NDA and/or Supervisory Memorandum related to the product approval, b) the product be given "class specific" labeling based on related marketed agents, or c) the sponsor should be asked to conduct a study in a non-rodent species.

3. If sufficient pharmacokinetic data are available, it is recommended that all interspecies dose comparisons included in the product label be based on AUC, $C_{max}$ or other relevant parameter, unless there is clear scientific justification for the use of another scaling method [redacted] If there is insufficient pharmacokinetic data to allow for interspecies dose comparisons at this time, the sponsor should be asked to develop this data.

III. Specific comments related to the product label follow:

1. It is recommended that the non-clinical reproductive toxicity study results which are included in the "CONTRAINDICATIONS" section of the proposed product label (see pages 4 and 5) be moved to the "Pregnancy" section of the product label under "PRECAUTIONS." The current placement of this information is: a) not in accordance with CFR 201.57 (d), which states that the 'contraindications' section of the label shall describe "known hazards and NOT theoretical possibilities", and b) the study results relate to negative effects observed in animal studies, the lack of effects not being critical to the safe use of the drug product (21CFR 201.57 Subparts b(1) and b(2)ii).

2. Under the heading of "Carcinogenesis, Mutagenesis and Impairment of Fertility" it is recommended that:
   - reference to the duration of drug treatment and reduced survival (approx. 13-19 months) be included in the discussion of the rat carcinogenicity study results.
   - the statement pertaining to pituitary tumors and histiosarcomas be revised to indicate whether the incidence of tumors increased with dose or was seen among all drug treatment groups.
   - the specific genotoxicity studies conducted with triptorelin should be identified in the discussion of the mutagenic and/or clastogenic effects of the drug.
   - if the effects of triptorelin on male fertility during or following the cessation of treatment were not studied, then the product label should indicate the lack of available risk information regarding possible fertility effects in males.
   - the discussions of fertility and multi-generation effects with triptorelin exposure should clearly define the period/duration of drug exposure and the doses tested.
3. Under the heading of "Pregnancy Category" it is recommended that:
   - the teratology study results currently included in the "CONTRAINDICATIONS" section of the label be moved to the "Pregnancy" section.
   - the discussion of the rat teratology study results should clearly define or distinguish the meaning of the terminology "embryotoxicity" and "fetotoxicity".
   - reference to "developmental toxicity" as an adverse fetal effect be eliminated or rewritten, as it does not appear to be adequately supported by the reproductive toxicology study results.

4. Under the heading of "Overdosage" it is suggested that the doses studied in mice and rats be provided, along with the multiplicity of the human dose.
5. Although the indication for triptorelin does not include lactating women, the product label should be revised to include a discussion of potential drug related hazards in "Nursing Mothers", in accordance with CFR 201.57 (8) iii

## IV Summary

A review of the action package for NDA 20-715, TRELSTAR® Depot Injection, suggests that the product may have undergone adequate toxicologic evaluation for approval for the requested indication (palliative treatment of prostate carcinoma). However, the omission of the toxicology study reviews/data from the NDA Review makes final evaluation of the NDA Action Package (and proposed actions related to product labeling) preliminary. Specific recommendations regarding product labeling are included in the preceding sections of this memorandum.

MAY 19 2000

**Memo**

5-18-2000

To: NDA 20-715

From: Krishan L. Raheja, Pharmacologist

This is to state that the Pharmacology review is essentially the same as was written and filed for the original NDA submission for Decapeptyl Depot in 1996.
Only minor changes now were made in the labeling, which have been agreed to by the sponsor and included in the present labeling.
Pharmacology has no objection to the approval of NDA 20-715 for the palliative treatment of advanced prostate cancer.

/S/

Krishan L. Raheja 5-18-2000

/S/ 5/19

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10-21-1996

NDA 20-715

Dabio R.P. SA
Martigny, Switzerland

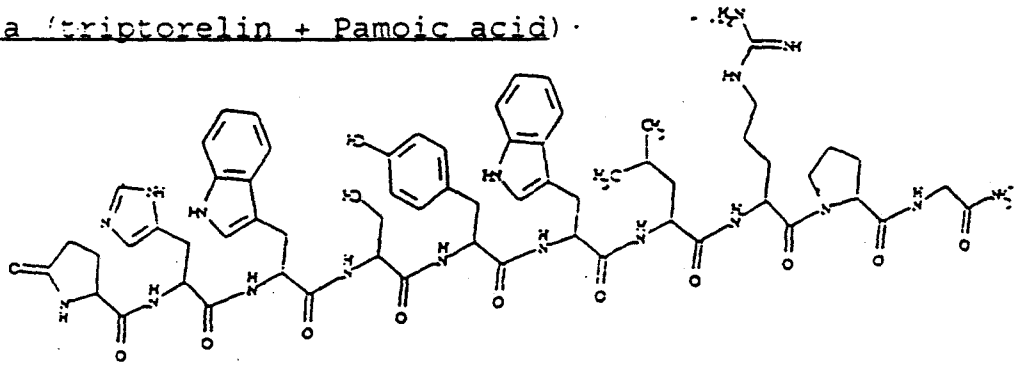
Submission dated: 6-24-1996 Received at CDER: 6-26-1996

## Pharmacology Review of Original NDA Submission

Drug name:

Established name: Triptorelin
Proprietary name: Decapeptyl depot
Code name: D-Trp -LHRH
Chemical name: Pyr-His-Trp-Ser-Tyr-D-Trp-Leu-Arg-Pro-Gly-NH
Pamoate salt

Structural formula (triptorelin + Pamoic acid)



pamoic acid
$C_{23}H_{16}O_6$

Molecular formula: C64 H84 N18 O13 . C23 H16 O6

Molecular weight: 1311.5 + 388.4 = 1699.9

Dosage form: Depot suspension

Route of administration: Intramuscular

Strength: 3.75 mg

Drug Product- Composition and dosage form:

Each vial of lyophilized drug product contains 3.75 mg of triptorelin pamoate incorporated into microgranules of poly(d,l-lactide-co-glycolide), along with carboxymethylcellulose sodium ( ) and polysorbate 80 ( ) plus mannitol excipient.

The composition per vial is as follows:

3.75 mg vial product:

| | |
|---|---|
| Triptorelin (free base units) (5.6 mg as triptorelin pamoate) | 3.75 mg |
| Poly(d,l-lactide-co-glycolide) | 170 mg |
| Mannitol, USP | 85 mg |
| Carboxymethylcellulose, USP | 30 mg |
| Polysorbate 80, USP (Tween 80) | 2 mg |
| Sterile water, USP | qsad |

Proposed indication: Palliative treatment of advanced carcinoma of the prostate.

Related INDs: filed with HFD-580 for prostate cancer and filed with

IND was originally submitted by Lederle Laboratories for triptorelin acetate (Decapeptyl microcapsules). The formulation of Decapeptyl was later changed from microcapsules to microgranules and salt was changed from acetate to pamoate. The IND was later transferred to on 10-16-1987.
It was stated that product (triptorelin pamoate) once approved, will be packaged and distributed in the U.S. by Pharmacia & Upjohn, Co. but not under the registered trade name Decapeptyl Depot.

Pharmacologic class of the drug:

Triptorelin pamoate, the active principle of Decapeptyl is a synthetic decapeptide agonist analog of the naturally occurring luteinizing hormone releasing hormone (LHRH), also called gonadotropin releasing hormone (GnRH).
The analog possesses greater potency than the natural hormone by virtue of substitution of D-amino acid for glycine at position 6, which is the link between the two bioactive portions of the peptide. The major difference between decapeptyl and other FDA approved LHRH agonists is that different D-amino acid substitution takes place at position 6 and all analogs retain those sequences of the LHRH decapeptide responsible for it biological activity as shown below for LHRH and LHRH agonists:

LHRH (Pyro)Glu-His-Trp-Ser-Tyr- Gly- Leu-Arg-Pro-Gly-NH2

leuprolide (pyro)Glu-His-Trp-Ser-Tyr- D-Leu- Leu-Arg-Pro-ethylamide

nafarelin (Pyro)Glu-His-Trp-Ser-Tyr- D-Nal(2)-Leu-Arg-Pro-Gly-NH2

Goserelin (Pyro)Glu-His-Trp-Ser-Tyr-D-Ser-(tBut)-Leu-Arg-Pro-Gly(Az)-NH2

tryptorelin (pyro)Glu-His-Trp-Ser-Tyr- D-Trp- Leu-Arg-Pro-Gly-NH2

The substitution of D-amino acid at position 6 makes the molecule resistant to cleavage by proteolytic enzymes, prolongs half-life, and thus increases biological potency relative to native LHRH.

The in-vitro LH releasing activity of primary cultures of rat anterior pituitary cells for leuprolide and triptorelin relative to LHRH was 30 and 100 fold respectively.

Rationale for the drug: LHRH is synthesized in the cell bodies of hypothalamic neurons and is secreted in a pulsatile pattern directly into the hypothalamic-hypophyseal portal circulation. At

the pituitary, it selectively stimulates the gonadotropes to synthesize and secrete gonadotropins i.e. LH and FSH which in turn stimulate the gonadal production of sex steroid hormones and gametogenesis.

An acute injection of LHRH or an LHRH agonist induces release of LH and FSH but continuous stimulation of LH secretion by repeated dose administration or by single administration of long acting LHRH agonists results in desensitization of gonadotropin secretion and gonadal suppression and decrease in testosterone production.

The induced chemical castration is the result of "down regulation" of pituitary receptors for LHRH, desensitization of pituitary gonadotroph cells, and reduction in gonadal receptors for LH and FSH.

Since the growth of prostate cancer is androgen dependent, the chemical castration induced by GnRH agonists, is a treatment option to orchiectomy and DES therapy.

Advantages of depot formulation over daily injections and orchiectomy:

The advantage of Decapeptyl depot formulation over daily injections is that the dose regimen is convenient. The advantage over orchiectomy is that it is reversible and it is claimed that patients have better psychological outlook.

Non-clinical pharmacology and toxicology:

Pharmacology has been mostly summarized from information taken directly from the literature. These studies describe 1) mechanism of action of LHRH, 2) desensitization of gonadotropin secretion with chronic stimulation of LH secretion by LHRH or LHRH agonists as demonstrated both in-vivo and in-vitro conditions, 3) potency of Decapeptyl relative of LHRH in-vitro and in-vivo, 4) activity of Decapeptyl against prostate tumors and 5) activity of Decapeptyl against non-prostate tumors.

Toxicology studies conducted consisted of 1) acute, 2) subacute, 3)chronic, 4)carcinogenicity, 5)developmental toxicity studies, 6)mutagenicity studies and 7) studies on the safety of drug carrier.

Other studies consisted of absorption, distribution, metabolism and excretion (ADME) and pharmacodynamic studies with triptorelin.

Sponsor has also provided 157 literature references.

All the pharmacology/toxicology/ADME studies have been reviewed in various submissions under [redacted] IND [redacted] Pertinent submissions pertaining to non-clinical pharmacology and toxicology include the original submission dated 6-18-1986, annual report dated 4-11-88, submission serial Nos 012 dated 9-27-1988, 032 dated 9-27-1990, 044 dated 11-15-1991, 050 dated 4-20-1993 and 051 dated 7-12-1993.

Under the original submission dated 6-18-1986, following preclinical studies were reviewed:

1. Pharmacology and pharmacokinetics

2. Toxicology:

a. A 2-month intramuscular toxicity study of [D-trp$^6$]-LH-RH in male and female Sprague-Dawley rats.

b. A 3-month toxicity study of CL 118,532 sustained release microcapsules and solutions after intramuscular administration to adult male rats.

c. A chronic toxicity study (6 monthly cycles) of CL 118,532 after intramuscular administration to male rats with a 4 month recovery phase.

d. Chronic (6 monthly cycles) study in dogs treated by the intramuscular route with sustained-release microcapsules of CL 118,532.

e. D-Trp$^{6}$-LH-RH: 6-months of subcutaneous tretament, two months of reversibility in rats.

f. Six month subcutaneous toxicity study of D-Trp$^{6}$-Lh-RH followed by a two month recovery period in Cebus apella (Capuchin) monkeys.

g. 6-month (197days) intramuscular toxicity study of D-Trp$^{6}$-LH-RH microcapsules in Beagle dogs.

Under the first annual report dated 4-11-1988, a study entitled "D-trep$^{6}$-LH-RH special preliminary subcutaneous pilot study in the rabbit" and an other entitled "treatment of experimental ovarian carcinoma with monthly injection of the agonist D-trp$^{6}$-Lh-RH" along with 3 mutagenicity studies (Ames test, in-vivo mouse micronucleus assay and in-vitro cytogenic assay measuring chromosome aberration frequencies in CHO cells) were reviewed.

A study entitled "D-Trp$^{6}$-LH-RH- special fertiility study in the rat by injection" was reviewed under submission serial No. 012 dated 9-27-1988.

The following 4 studies were reviewed under submission serial No. 032 dated 9-27-1990:

a. A chronic (6 month) toxicity study in the dog with Decapeptyl microgranules via intramuscular injection.

b. A chronic (6 month) toxicity study in the rat with Decapeptyl via intramuscular injection.

c. A segement II teratology study in rats with Decapeptyl.

d. A segment II teratology study in mice with Decapeptyl

Two PK studies entitled " A pharmacokinetic study in the dog with decapeptyl microgranules via intramuscular injection with special focus on testosterone, FSH and JH levels" and
"A pharmacokinetic study in the rat with decapeptyl microgranules via intramuscular injection with special focus on testosterone, FSH and LH levels" were reviewed under submission seril No. 044

dated 11-15-1991.

A mouse carcinogenicity study entitled "An eighteen month oncogenicity study in mice with decapeptyl microgranules via intramuscular injection" and a rat carcinogenicity study entitled "A 24 month carcinogenicity study in the rat with decapeptyl microgranules via intramuscular injection" were reviewed under submission serial #s 050 and 051 dated 4-20-1993 and 7-12-1993 respectively.

It should be pointed out that in the rat carcinogenicity study, forestomach lesions were predominantly observed in the drug treated animals. The sponsor initially stated that the frequency of occurrence of these lesions in the treated animals was similar to those in the non-treated controls, a statement sponsor later could not substantiate. Also the incidence and frequency of sertoliform cells in the ovaries was reported only for the treated animals.

Sponsor however, has provided an explanation for the forestomach lesions and occurrence of sertoliform cells in the ovaries of treated animals to the satisfaction of pharmacology.

Also, excessive mortality was observed in the rat carcinogenicity study. However, after review of the data, it was decided that since the Division has had considerable experience with this class of drugs, limited data from the rat carcinogenicity study and complete data from the mouse carcinogenicity study are sufficient to support the safety profile of Decapeptyl. Thus Pharmacology considered the submitted studies to be valid and fulfill our requirements for carcinogenicity studies and sponsor was accordingly informed on 4-27-1992. Carcinogenicity data for the rat and mouse studies have been submitted to Biometrics for statistical review.

Mouse carcinogenicity data were submitted to the Exec. CAC and were reviewed and approved at the May 3, 1994 meeting.

The carcinogenic profile of Decapeptyl was essentially similar to that observed for other approved GnRH agonist analogs.

In a meeting with the sponsor on 7-6-94, to review the over all status of pharmacology/toxicology, it was decided that studies submitted to the IND were sufficient to support a NDA.

Clinical experience with Decapeptyl:

Human pharmacokinetics and bioavailability studies consisted of 1) protein binding, 2) bioavailability/bioequivalence, 3) pharmacokinetics, 4) dose proportionality and 5) special populations: renal and hepatic disease.

It was stated that triptorelin acetate has been approved for marketing for the palliative treatment of prostate carcinoma in over 60 countries. Also pamoate salt of triptorelin (Decapeptyl) has been approved in France and has been marketed in Brazil since 1993.

The safety and effectiveness of triptorelin acetate is based on 37 clinical pharmacology studies, 4 controlled and 20 uncontrolled studies performed in patients with advanced prostatic carcinoma. In addition there are 30 additional studies in which triptorelin acetate was employed for indications other than prostatic carcinoma. Advantage of triptorelin pamoate depot suspension is that it does not require [redacted] for manufacture.

Labeling: Labeling essentially conforms to those for other approved GnRH agonists i.e.Lupron (leuprolide acetate for depot suspension), Zoladex (goserelin acetate implant), Synarel (nafarelin acetate nasal solution) and Supprelin (histrelin acetate injection).

However, while for the above approved GnRH agonists it is mentioned in the labeling under Contraindications that these analogs are contraindicated in those patients who have a known hypersensitivity to LHRH, LHRH agonist analogs or any components of the product, for Decapeptyl it is stated that three cases of anaphylactic shock and two cases angioedema have been reported that were related to triptorelin. Although it would suggest that the safety profile of triptorelin pamoate is different from other approved GnRH agonists, it could be due to more careful

monitoring of adverse effects or due to greater pharmacologic potency of Decapeptyl depot compared to other GnRH agonist analogs.

Also while ~~for~~ the approved GnRH agonists under the Precaution section of labeling, statements are made that either no drug interaction studies were conducted or none reported, for triptorelin, it was stated that hyperprolactinemic drugs should not be prescribed concomitantly with Decapeptyl Depot since hyperprolactinemia reduced the number of pituitary GnRH receptors. Although not mentioned one will expect similar interaction with other GnRH agonists.

Recommendations: Based on review of the submitted literature and preclinical data along with an extensive clinical experience with Decapeptyl depot, Pharmacology considers it safe and recommends approval of NDA 20-715 for the palliative treatment of prostatic carcinoma.

/S/ 10/21/96

Krishan L. Raheja, D.V.M.,Ph.D

/S/ 10/22

Original NDA 20-715
HFD-345
HFD-580
HFD-580/A.Jordan/M.Shames
HFD-580/K.Raheja, 10-21-1996, N20715.ori