

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-437

PHARMACOLOGY REVIEW(S)



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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 22,437
DATE RECEIVED BY CENTER: September 2008 and September 2009
PRODUCT: Trelstar® (triptorelin pamoate for injectable suspension) 22.5 mg
INTENDED CLINICAL POPULATION: Palliative treatment of advanced prostate cancer
APPLICANT: Watson Laboratories, Inc.
REVIEW DIVISION: Division of Drug Oncology Products
PHARMACOLOGY/TOXICOLOGY
REVIEWER: Wei Chen, Ph.D.
PHARMACOLOGY/TOXICOLOGY
SUPERVISOR: Haleh Saber, Ph.D.
DIVISION DIRECTOR: Robert Justice, MD
PROJECT MANAGER: Kim Robertson

Date of review submission to DARRTS: 16 March 2010

PHARMACOLOGY/TOXICOLOGY REVIEW

INTRODUCTION AND DRUG HISTORY

Triptorelin is a synthetic decapeptide agonistic analog of gonadotropin releasing hormone (GnRH). Triptorelin was previously approved for the palliative treatment of advanced prostate cancer for both the 3.75 mg (NDA 20,715) and 11.25 mg strengths (NDA 21,288). In September 2008, the Applicant submitted a new NDA (22,437) for a 24-week administration of the drug; the submission contained a PLR version of the label which appeared to be incomplete. In April 2009, the FDA informed the Applicant to submit a revised integrated product insert label that reflects information on all 3 triptorelin strengths. A new version of the label was submitted early in May 2009. Discussions below reflect changes made to the May 2009 version of the PLR label.

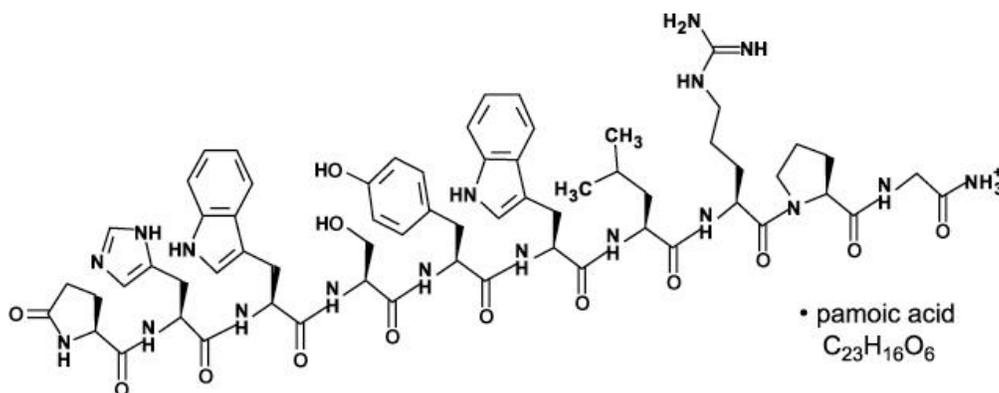
Drug:

Trade name: **TRELSTAR®** (triptorelin pamoate for injectable suspension)

Chemical name: 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-tryptophyl-L-leucyl-L-arginyl-L-prolylglycine amide (pamoate salt)

Molecular formula/molecular weight: $C_{64}H_{82}N_{18}O_{13} \cdot C_{23}H_{16}O_6/1699.9$

Structure:



Pharmacologic class: gonadotropin releasing hormone (GnRH) agonist

Intended clinical population: the palliative treatment of advanced prostate cancer

Clinical formulation: injectable suspension, 3.75 mg, 11.25 mg, 22.5 mg

Route of administration: intramuscular injection

The following section will contain the Applicant's proposed wording for the label followed by the FDA recommendation with a rationale for the recommended changes. Of note, most changes were made to comply with 21CFR 201 on PLR content and formatting and recent practices.

The Applicant proposed pharmacologic class for the HIGHLIGHT section of the label:

(b) (4) agonist

FDA recommends:

gonadatropin releasing hormone (GnRH) agonist

Rationale

“Gonadatropin releasing hormone (GnRH) agonist” is an established pharmacologic class for this drug and other drugs of this class. The concept is further described in the following Guidance: Labeling for Human Prescription Drug and Biological Products — Determining Established Pharmacologic Class for Use in the Highlights of Prescribing Information.

The Applicant proposed

4 CONTRAINDICATIONS

TRELSTAR is contraindicated in individuals with a known hypersensitivity to triptorelin or any other component of the product, other (b) (4) agonists or (b) (4)

TRELSTAR is contraindicated in women who are or may become pregnant (b) (4)

(b) (4) TRELSTAR may cause fetal harm when administered to a pregnant woman.

FDA recommends

4 CONTRAINDICATIONS

4.1 HYPERSENSITIVITY

TRELSTAR is contraindicated in individuals with a known hypersensitivity to triptorelin or any other component of the product, or other GnRH agonists or GnRH [see *Warnings and Precautions (5.1)*].

4.2 PREGNANCY

TRELSTAR may cause fetal harm when administered to a pregnant woman. Expected hormonal changes that occur with TRELSTAR treatment increase the risk for pregnancy loss and fetal harm when administered to a pregnant woman [see *Use in Specific Populations (8.1)*]. TRELSTAR is contraindicated in women who are or may become

pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Rationale

Changes recommended are in compliance with CFR and current practices. Presently, hormonal agents such as GnRH agonists are assigned Pregnancy Category X, if indicated in male malignancies only. This is mainly due to the known embryofetal effects (lethality) associated with these drugs and the lack of benefit to pregnant females.

The Applicant proposed

8.1 PREGNANCY

Pregnancy Category X.

TRELSTAR is contraindicated in women who are or may become pregnant while receiving the drug

(b) (4)



FDA recommends

8.1 PREGNANCY

Pregnancy Category X [see 'Contraindications' section].

TRELSTAR is contraindicated in women who are or may become pregnant while receiving the drug. Expected hormonal changes that occur with TRELSTAR treatment increase the risk for pregnancy loss. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Studies in pregnant rats administered triptorelin at doses of 2, 10, and 100 mcg/kg/day (approximately equivalent to 0.2, 0.8, and 8 times the estimated human daily dose based on body surface area) during the period of organogenesis demonstrated maternal toxicity and embryo-fetal toxicities. Embryo-fetal toxicities consisted of pre-implantation loss, increased resorption, and reduced mean number of viable fetuses at the high dose.

Teratogenic effects were not observed in viable fetuses in rats or mice. Doses administered to mice were 2, 20, and 200 mcg/kg/day (approximately equivalent to 0.1, 0.7, and 7 times the estimated human daily dose based on body surface area).

Rationale

Changes recommended are based on the CFR, current practices, and to more accurately capture embryo-fetal effects. Description of observed toxicities at different given doses

was added by the Applicant in response to FDA's request conveyed during the review process. In addition, the present label contains 3 dosing schedules, every 4-week, every 12-week, and every 24-week dose administration; however the animal studies were conducted by daily dosing. Therefore, the animal to human dose extrapolation is calculated using an estimated daily human dose, based on the presumption of a steady daily release of the drug in humans.

The Applicant proposed

(b) (4)

FDA recommends deleting this section.

Rationale

(b) (4)

The Applicant proposed

8.3 NURSING MOTHERS

TRELSTAR (b) (4) is not indicated for use in women [*see Indications and Usage (1)*].

FDA recommends

8.3 NURSING MOTHERS

TRELSTAR is not indicated for use in women [*see Indications and Usage (1)*]. It is not known if triptorelin is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from TRELSTAR, a decision should be made to either discontinue nursing, or discontinue the drug taking into account the importance of the drug to the mother.

Rationale

Based on current practices, including recommendation by the Maternal Health Team to include the information described in 21CFR201.57.

The Applicant proposed

10 OVERDOSAGE

There is no experience of overdosage in clinical trials. In single dose toxicity studies in mice and rats, the subcutaneous LD₅₀ of triptorelin was 400 mg/kg in mice and 250 mg/kg in rats, approximately (b) (4) times, respectively, (b) (4)

If overdosage occurs, therapy should be discontinued immediately and the appropriate supportive and symptomatic treatment administered.

FDA recommends

10 OVERDOSAGE

There is no experience of overdosage in clinical trials. In single dose toxicity studies in mice and rats, the subcutaneous LD₅₀ of triptorelin was 400 mg/kg in mice and 250 mg/kg in rats, approximately 500 and 600 times, respectively, the estimated monthly human dose based on body surface area. If overdosage occurs, therapy should be discontinued immediately and the appropriate supportive and symptomatic treatment administered.

Rationale

The animal to human dose extrapolation (b) (4) fold difference) does not correspond to either the estimated daily or monthly human dose on the basis of body surface area. The Applicant was asked to correct the numbers. The Applicant chose the 500 and 600 fold values for dose extrapolation based on the estimated monthly human dose. FDA agreed.

12.1 MECHANISM OF ACTION

Triptorelin is a (b) (4)

FDA recommends

12.1 MECHANISM OF ACTION

Triptorelin is a synthetic decapeptide agonist analog of gonadotropin releasing hormone (GnRH). Comparative *in vitro* studies showed that triptorelin was 100-fold more active than native GnRH in stimulating luteinizing hormone release from monolayers of dispersed rat pituitary cells in culture and 20-fold more active than native GnRH in displacing ¹²⁵I-GnRH from pituitary receptor sites. In animal studies, triptorelin pamoate was found to have 13-fold higher luteinizing hormone-releasing activity and 21-fold higher follicle-stimulating hormone-releasing activity compared to the native GnRH.

Rationale

Information on the mechanism of action was placed under “Description”, i.e. section 11. This information should be under 12.1. Further changes were made to remove promotional wording.

Discussions on section 13.1 were mainly on fertility; hence only the paragraph on fertility will be presented below.

The Applicant proposed

13.1 CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

[REDACTED] (b) (4)

No studies were conducted to assess the effect of triptorelin on male fertility.

FDA recommends

13.1 CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

After 60 days of subcutaneous treatment followed by a minimum of four estrus cycles prior to mating, triptorelin, at doses of 2, 20, and 200 mcg/kg/day in saline (approximately 0.2, 2, and 16 times the estimated human daily dose based on body surface area) or 2 monthly injections as slow release microspheres (~20 mcg/kg/day), had no effect on the fertility or general reproductive function of female rats.

No studies were conducted to assess the effect of triptorelin on male fertility.

Rationale

A fertility study does not generally provide information needed to adequately address the effects on the offspring. The Applicant was asked to either delete the information on F1 or to provide justification for the statement. The Applicant chose to delete the sentence. Additional information was added to this section for further clarification, e.g. information on route and schedule of administration is added.

Application
Type/Number

Submission
Type/Number

Submitter Name

Product Name

NDA-22437

ORIG-1

WATSON
LABORATORIES
INC

TRELSTAR (b) (4)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WEI CHEN
03/16/2010

HALEH SABER
03/16/2010