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APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-288

Pharmacology Review(s)

N21-288.000

REVIEW AND EVALUATION OF PHARMACOLOGY/TOXICOLOGY DATA:

KEY WORDS: Triptorelin pamoate, Trelstar LA, prostate cancer
Reviewer Name: Krishan L. Raheja
Division Name: DRUDP
HFD#: 580
Review Completion Date: 8-21-2000

Review number: 1
IND/NDA number: NDA 21-288
Serial number/date/type of submission: 000/6-29-2000/Original submission
Information to sponsor: Yes ( ) No (*)
Sponsor (or agent): Debio Recherche Pharmaceutique SA, Switzerland
Manufacturer for drug substance:

Drug:

Code Name: D-Trp^6-LHRH
Generic Name: Triptorelin pamoate for injection suspension
Trade Name: Trelstar LA
Chemical Name: Pyr-His-Trp-Ser-Tyr-D-Trp-Leu-Arg-Pro-Gly-NH_2 pamoate salt
CAS Registry Number:
Molecular Formula/ Molecular Weight: $C_{64}H_{82}N_{18}O_{13}$. $C_{23}H_{16}O_6$/ 1311,5 + 388.4 = 1699.9

Structure: see NDA 20-715 review dated 10-21-1996

Relevant INDs/NDAs/DMFs: NDA 20-715 (1-month formulation of triptorelin pamoate)

Drug Class: GnRH agonist

Indication: Palliative treatment of advanced prostate cancer

Clinical formulation: Depot suspension, 11.25 mg

Composition and dosage form: Each vial of lyophilized drug product contains 11.25 mg of triptorelin pamoate (free base) incorporated into microgranules with 145 mg poly d,l-lactide-co-glycolide along with 85 mg mannitol, 30 mg carboxymethylcellulose and 2 mg polysorbate 80.

Route of administration: Intramuscular every 84 days

Proposed clinical protocol or Use: For the palliative treatment of advanced prostate cancer

Previous clinical experience: Sponsor has previously conducted clinical studies in Europe using 1-month controlled release formulation of triptorelin acetate microspheres 3.75 mg administered every 28 days. Subsequently, a 1-month sustained release formulation of 3.75 mg triptorelin pamoate (Trelstar Depot) was tested and approved for marketing in the United States.

Triptorelin 3-month formulation (11.25 mg) is approved in several countries for various indications. It is used either as lyophilized microparticles or lyophilized microgranules. The ratio of glycolic/lactic acid in poly(glycolic/lactic acid) is 1:1 for lyophilized microparticles and 1:3 for lyophilized granules.

Sponsor also has conducted following four clinical studies with the proposed 3-month formulation to support the safety of Trelstar LA in men with advanced prostate cancer.

DEB-96-TRI-01, a comparative clinical study of triptorelin pamoate 3-month and 1-month formulations.

UK DCP 94-090, a Phase 2 comparative three-month, bioequivalence and pharmacokinetic study of triptorelin pamoate 11.25 mg and triptorelin acetate 3.75 mg.

DEB-95-TRI-01, comparison of 2 different formulations of triptorelin 11.25 mg.

DEB-99-TRI-01, a Phase I-II comparative pharmacokinetic study.

Disclaimer -- use of sponsor's material

Introduction and drug history: Triptorelin is a synthetic decapeptide agonist analog of luteinizing hormone releasing hormone (LH-RH or GnRH). It is intended for the palliative treatment of prostate cancer as other approved GnRH agonists i.e. leuprolide (Lupron) and gosarelin (Zoldex).

Studies reviewed within this submission: The PK profiles of the 3-month (11.25 mg) and 1-month (3.75 mg) triptorelin pamoate formulations were compared in the 9-month clinical trial (study N0. DEB-96-TRI-01). The 3-month formulation was injected IM every 84 days (3 injections) and the 1-month formulation was injected every 28 days (9 injections). The results are shown in table below:

	$AUC_{1\text{-}85\ days}$ ng.h/ml	$AUC_{85\text{-}169\ days}$ ng.h/ml	$AUC_{169\text{-}253\ days}$ ng.h/ml	$C_{max\ (1\text{-}85days)}$ ng/ml	$C_{max\ (85\text{-}169days)}$ ng/ml	$C_{max\ (169\text{-}253days)}$ ng/ml
3-month formulation Mean + SD Range	2226 + 1.2	2152 + 1.3	**2428 + 1.4**	37.1 + 1.3	44.0 + 1.3	48.5 + 1.4
1-month formulation Mean + SD Range	Not	Not applicable	**2375 + 1.4**	15.2 + 1.4	19.5 + 1.4	21.3 + 1.2

N= 13 for 3-month formulation and 14 for 1-month formulation. T_{max} ranged from . hours for the 3-month formulation and 2 for the 1-month formulation.

Triptorelin serum levels were assessed over a 48 hour period following injection on Days 1, 85 and 169. Additional samples were also collected in the 1-month formulation patient subset on Day 197 and 225 to compute an $AUC_{169\text{-}253\ days}$ for the 1-month formulation in order to calculate the relative bioavailability of the 3-month formulation vs the 1-month formulation at steady state.

Results: Both formulations had similar bioavailability of triptorelin over the last 3 months of treatment based on $AUC_{169\text{-}253\ days}$. C_{max} was more than 2 times higher for the 3-month formulation than for the 1-month formulation. The relative bioavailability of the two formulations was similar.

Thus based on sytemic exposure at steady state level, pharmacodynamic and adverse events would be expected to be similar for the 3-month and 1-month formulation. As such the preclinical studies conducted to support the approval of 1-month formulation are adequate for the proposed 3-month formulation.

Studies not reviewed within this submission: All pharmacology/toxicology studies referred to NDA 20-715.

Protein binding: To determine the binding behavior of triptorelin pamoate to proteins, an in vitro study was performed in which blood was taken 4 hours after IM administration of 3.75 mg Trelstar to 6 healthy male volunteers. While nafarelin is reported to bind to proteins to a much greater extent (70-80%) than native LHRH (10-20%), and leuprolide binds to proteins to the same extent as native LHRH, no binding components were present in the sera of volunteers administered Trelstar.

Nonclinical pharmacology/toxicology: referred to NDA 20-715

OVERALL SUMMARY AND EVALUATION:

Introduction: Triptorelin is a synthetic decapeptide agonist analog of luteinizing hormone releasing hormone (LHRH or GnRH) with greater potency than the naturally occurring LHRH. It is an inhibitor of gonadotropin secretion when given continuously. Following a transient surge in circulating levels of LH and FSH, it causes a marked reduction of testicular and ovarian steroidogenesis. In men a reduction of serum testosterone level seen in surgically castrated men is obtained. Consequently tissues and functions that depend on testosterone for maintenance become quiescent.

Safety Evaluation: Based on the results of clinical studies with 1-month Trelstar formulation conducted in Europe and United States, proposed 3-month formulation seems safe. Also 11.25 mg formulation is approved in various countries outside the United Stated for prostate cancer, endometriosis, breast cancer and precocious puberty indications.

Clinical Relevance of Safety Issues: none

Other Clinically Relevant Issues: none

Conclusions: Trelstar is safe for the proposed indication

Communication Review:

- Labeling Review (NDA): Label is similar to that approved for the 1- month Trelstar formulation.
- Investigator's Brochure/Informed consent review (IND):

RECOMMENDATIONS: Based on results of the preclinical studies submitted to support approval of 1-month triptorelin pamoate formulation along with extensive available clinical

efficacy and safety data, Pharmacology recommends approval of Trelstar LA, 3-month triptorelin pamoate formulation for the palliative treatment of advanced prostate cancer.

Internal comments:
External Recommendations (to sponsor): none
Draft letter Content for Sponsor:
Future development or NDA issues: If triptorelin will be used for any benign male indication, male return to fertility study will be requested.

Reviewer signature/team leader signature [Concurrence/Non-concurrence]

cc: HFD 580/A.Jordan/J.Best
Draft date (# of drafts):
Memorandum of Non-concurrence (if appropriate, attached):
Addendum to review (if necessary):
Appendix/attachments: Copy of NDA 20-715 review