CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19726/S24

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Dunson

JUN 24 1998

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW
Division of Pharmaceutical Evaluation II

NDA 19-726

SUBMISSION DATE: August 11, 1997

Zoladex® 3.6 mg 1 Month-Depot
(Goserelin Acetate Implant)
Zeneca Pharmaceuticals, Inc.
Wilmington, DE

REVIEWER: Angelica Dorantes, Ph.D.

TYPE OF SUBMISSION: NDA- Clinical Supplement No. 024

BACKGROUND:

Zoladex (goserelin acetate implant) is a synthetic agonist analog of the naturally occurring hormone known as luteinizing hormone-releasing hormone (LHRH). The compound differs from the naturally occurring hormone in substitutions made at positions 6 and 10 of the peptide chain. The pharmacological effects of Zoladex result from occupation of LHRH receptors on the pituitary gland. Zoladex acts on the pituitary receptors of the hypothalamic-pituitary-gonadal axis, causing an initial stimulatory effect followed by down-regulation of gonadotropin receptors and subsequent reduction in luteinizing hormone (LH) secretion and suppression of serum testosterone to castrate levels.

CURRENT INDICATIONS:

The original NDA 19-726 for Zoladex® 3.6 mg 1-month Depot (goserelin acetate) was approved for the palliative treatment of advanced carcinoma of the prostate on December 29, 1989. Approval for the treatment of endometriosis was obtained on February 2, 1993 under NDA 19-726/S-005, for the treatment of breast cancer on December 18, 1995 under NDA 20-515, and for the treatment of endometrial thinning on June 27, 1997 under NDA 19-726/S-018.

CURRENT SUBMISSION:

This supplemental application (No. 024) to NDA 19-726 dated August 11, 1997 consists of;

- Published results of a single clinical trial [RTOG 8610; Pilepich, et al; Urology 1995;45(4):616-62] sponsored by the National Cancer Institute and conducted by the Radiation Therapy Oncology Group (RTOG). The results of Trial RTOG 8610 are included in this Supplement to support the use of Zoladex

in combination with an antiandrogen for the management of locally confined Stage T2b through T4 (Stage B2-C) carcinoma of the prostate when combined with radiotherapy.

- A revised version of Zoladex 3.6 mg 1 Month-Depot labeling which includes clinical information from Trial RTOG 8610 for the additional proposed indication.

TRIAL RTOG 8610 SUMMARY

Reference: "Androgen Deprivation with Radiation Therapy Compared with Radiation Therapy alone for Locally Advanced Prostatic Carcinoma: A Randomized Comparative Trial of Radiation Therapy Oncology Group", Pilepich MV, Krall JM, Al-Sarraf M, John MJ, Doggett RLS, Sause WT, et al., Urology 1995;45(4):616-23.

The RTOG 8610 trial was a randomized, controlled trial involving 471 men with large Stage T2b to T4 (B2-C) prostate tumors but without evidence of osseous metastases. Trial RTOG 8610 evaluated the use of CAB (complete androgen blockade) using Zoladex and flutamide before and during radiotherapy. The results of this trial showed that Zoladex plus flutamide combined with radiotherapy significantly ($p<0.01$) increased local control and disease-free survival in patients with locally confined Stage T2b to T4 (B2-C) prostate carcinoma when compared with pelvic irradiation alone. The trial showed Zoladex implant to be well tolerated and effective for use in combination with an antiandrogen for the management of locally confined prostate cancer when used before and during radiotherapy.

Based on the results of Trial RTOG 8610, the sponsor proposes in this supplement the use of Zoladex in combination with an antiandrogen to achieve complete androgen blockade. This combined pharmacological effect before and during radiation therapy, can lead to increase control of the primary tumor (i.e., the LHRH-A lowers the level of serum testosterone from the testes. The antiandrogen blocks the androgen receptors, thus decreasing the effects of both the residual testicular testosterone present after LHRH-A therapy and the testosterone produced by the adrenal gland).

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) has reviewed Supplement No. 024 to NDA 19-726 for Zoladex® 3.6 mg 1-month Depot which was submitted on August 11, 1997. The Reviewer Comments for this submission are as follows;

1. This clinical supplement to NDA 19-726 does not include any new clinical pharmacology and biopharmaceutic information for this product. Therefore, no additional recommendations to the ones given in the previous approvals are made at this time.

2. This supplement does not include any drug-drug interaction information for the studied combination of Zoladex and flutamide. Also, no drug-interaction information is provided for any other antiandrogen that may be given in combination with Zoladex. This lack of drug-drug information is clearly indicated in Zoladex labeling **"No formal drug-drug interaction studies have been performed"**.

3. It should be noted that the Drug-Drug Interaction subsection of EULEXIN® (flutamide) labeling includes the statement **"Interactions between EULEXIN capsules and LHRH agonists have not occurred"**. Because the same clinical study (Trial RTOG 8610) was used in EULEXIN's labeling to support the combination therapy EULEXIN-LHRH, it appears to be appropriate to recommend that a similar drug-drug interaction statement be included in Zoladex labeling.

4. With respect to the proposed labeling (see Attachment I), no major changes for the additional clinical indication sought herein were made to the **Pharmacokinetic** subsection of the **CLINICAL PHARMACOLOGY** section of the labeling, therefore, it is acceptable. However, it is recommended that **i)** the **"Special Populations"** subsection be reformatted as appropriate to include Zoladex's renal and hepatic information under the subheadings **"Renal Insufficiency"** and **"Hepatic Insufficiency"**, and **ii)** the **"Dug-Drug Interactions"** subsection be modified as follows: No formal drug-drug interaction studies have been performed. However, published information indicates that interactions between EULEXIN (i.e., flutamide) and LHRH (i.e., Zoladex) have not occurred.

Please convey the Recommendation and Comment No. 4 as appropriate to the sponsor.

/S/ 6/23/98

Angelica Dorantes, Ph.D.
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

RD Initialed by John Hunt. JPH 6/17/98

FT signed by John Hunt. /S/ 6/24/98

Dunson

JUN 24 1998

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW
Division of Pharmaceutical Evaluation II

NDA 20-578 **SUBMISSION DATE:** August 11, 1997

Zoladex®10.8 mg 3-month Depot
(Goserelin Acetate Implant)
Zeneca Pharmaceuticals, Inc.
Wilmington, DE

REVIEWER: Angelica Dorantes, Ph.D.

TYPE OF SUBMISSION: NDA- Clinical Supplement No. 003

BACKGROUND:

The original NDA 20-578 for Zoladex® 10.8 mg 3-month Depot (goserelin acetate) was approved by the Agency on January 11, 1996 for the palliative treatment of advanced carcinoma of the prostate.

Zoladex (goserelin acetate implant) is a synthetic agonist analog of the naturally occurring hormone known as luteinizing hormone-releasing hormone (LHRH). The compound differs from the naturally occurring hormone in substitutions made at positions 6 and 10 of the peptide chain. The pharmacological effects of Zoladex result from occupation of LHRH receptors on the pituitary gland. Zoladex acts on the pituitary receptors of the hypothalamic-pituitary-gonadal axis, causing an initial stimulatory effect followed by down-regulation of gonadotropin receptors and subsequent reduction in luteinizing hormone (LH) secretion and suppression of serum testosterone to castrate levels.

CURRENT SUBMISSION:

This supplemental application (No. 003) to NDA 20-578 dated August 11, 1997 consists of;

- Published results of a single clinical trial [RTOG 8610; Pilepich, et al.] sponsored by the National Cancer Institute and conducted by the Radiation Therapy Oncology Group (RTOG). The results of Trial RTOG 8610 are included in this Supplement to support the use of Zoladex in combination with an antiandrogen for the management of locally confined Stage T2b through T4 (Stage B2-C) carcinoma of the prostate when combined with radiotherapy.

- A revised version of Zoladex 10.8 mg 3-month Depot labeling which includes proposed clinical information from Trial RTOG 8610 for the additional indication.

TRIAL RTOG 8610 SUMMARY:

Reference: "Androgen Deprivation with Radiation Therapy Compared with Radiation Therapy alone for Locally Advanced Prostatic Carcinoma: A Randomized Comparative Trial of Radiation Therapy Oncology Group", Pilepich MV, Krall JM, Al-Sarraf M, John MJ, Doggett RLS, Sause WT, et al., Urology 1995;45(4):616-23.

The RTOG 8610 trial was a randomized, controlled trial involving 471 men with large Stage T2b to T4 (B2-C) prostate tumors but without evidence of osseous metastases. Trial RTOG 8610 evaluated the use of CAB (complete androgen blockade) using Zoladex and flutamide before and during radiotherapy. The results of this trial showed that Zoladex plus flutamide combined with radiotherapy significantly ($p<0.01$) increased local control and disease-free survival in patients with locally confined Stage T2b to T4 (B2-C) prostate carcinoma when compared with pelvic irradiation alone. The trial showed Zoladex implant to be well tolerated and effective for use in combination with an antiandrogen for the management of locally confined prostate cancer when used before and during radiotherapy.

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) has reviewed Supplement No. 003 to NDA 20-578 for Zoladex® 10.8 mg 3-month Depot which was submitted on August 11, 1997. The Reviewer Comments for this submission are as follows;

1. This clinical supplement to NDA 19-726 does not include any new clinical pharmacology and biopharmaceutic information for this product. Therefore, no additional recommendations to the ones given in the previous approvals are made at this time.

2. This supplement does not include any drug-drug interaction information for the studied combination of Zoladex and flutamide. Also, no drug-interaction information is provided for any other antiandrogen that may be given in combination with Zoladex. This lack of drug-drug information is clearly indicated in Zoladex labeling **"No formal drug-drug interaction studies have been performed"**.

3. It should be noted that the Drug-Drug Interaction subsection of EULEXIN® (flutamide) labeling includes the statement **"Interactions between EULEXIN capsules and LHRH agonists have not occurred"**. Because the same clinical study (Trial RTOG 8610) was used to support the combination therapy EULEXIN-LHRH in EULEXIN's labeling, it appears to be appropriate to recommend that a similar drug-drug interaction statement be included in Zoladex labeling.

4. With respect to the proposed labeling, it is recommended that the following changes be incorporated in the **Pharmacokinetic** section of the labeling:

Comment:

- TABLE 1 SHOULD BE INSERTED HERE. ALSO IN TABLE 1, STANDARD ERROR VALUES SHOULD BE REPLACED WITH STANDARD DEVIATION (SD) VALUES.

Serum goserelin concentrations in prostate cancer patients administered three 3.6 mg depots followed by one 10.8 mg depot are displayed in Figure 1. The profiles for both formulations are primarily dependent upon the rate of drug release from the depots. For the 3.6 mg depot, mean concentrations gradually rise to reach a peak of about 3 ng/mL at around 15 days after administration and then decline to approximately 0.5 ng/mL by the end of the treatment period. For the 10.8 mg depot, mean concentrations increase to reach a peak of about 8 ng/mL within the first 24 hours and then decline rapidly up to Day 4. Thereafter, mean concentrations remain relatively stable in the range of about 0.3 to 1 ng/mL up to the end of the treatment periods.

Comment:

- FIGURE 1 SHOULD BE INSERTED HERE

Administration of four Zoladex 10.8 mg depots to patients with prostate cancer resulted in testosterone levels that were suppressed to and maintained within the range normally observed in surgically castrated men (0-1.73 nmol/L or 0-50 ng/dL), over the dosing interval in approximately 91% (145/160) of patients studied. In 6 of 15 patients that escaped from castrate range, serum levels of testosterone were maintained below 2.0 nmol/L (58 ng/dL) and in only one of the 15 patients did the depot completely fail to

maintain serum testosterone levels within the castrate range over a 336-day period (4 depot injections). In the 8 additional patients, a transient escape was followed 14 days later by a level within the castrate range.

Distribution: The apparent volume of distribution determined after subcutaneous administration of 250 µg aqueous solution of radiolabeled goserelin was 44.1 ± 13.6 liters for healthy males. The plasma protein-binding of goserelin was found to be about 27%.

Metabolism: Metabolism of goserelin, by hydrolysis of the C-terminal amino acids, is the major clearance mechanism. The major circulating component in serum appeared to be the 1-7 fragment, and the major component presented in the urine of one healthy male volunteer was the 5-10 fragment. The metabolism of goserelin in humans yields a similar but narrow profile of metabolites found in other species. All metabolites found in humans have also been found in toxicological species.

Excretion: Clearance of goserelin following subcutaneous administration of a radiolabeled solution of goserelin was very rapid and occured via a combination of hepatic and urinary excretion. More than 90% of a subcutaneous radiolabeled solution formulation dose of goserelin was excreted in urine. Approximately 20% of the dose recovered in urine was accounted for by unchanged goserelin.

Special Populations:

The information included in this section is appropriate and no changes are recommended.

Drug-Drug Interactions: No formal drug-drug interaction studies have been performed. However, published literature indicates that interactions between EULEXIN (i.e., flutamide) and LHRH (i.e., Zoladex) have not occurred.

Please convey the Recommendation and Labeling Comment No. 4 as appropriate to the sponsor.

/S/ 6/23/98

Angelica Dorantes, Ph.D.
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

RD Initialed by John Hunt._____ IPH 6/17/98

FT signed by John Hunt._____ /S/ 6/24/98

cc: NDA 20-578, HFD-580 (Hirsch, Dunson), HFD-870 (Chen, Dorantes), CDR (Barbara Murphy for Drug).