CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19726/S18

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

JAN 13 1997

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS

NDA: 19-726

Compound: Zoladex® 3.6 mg 1-month Depot (goserelin acetate implant)

Submission Dates: 6/28/96 (S-018)

Sponsor: Zeneca Pharmaceuticals, Inc.

Types of Submission: Supplement (new indication)

Code: 3S

Reviewer: K. Gary Barnette, Ph.D.

Background:
Zoladex®, goserelin acetate, is a potent synthetic decapeptide analogue of luteinizing hormone releasing hormone (LHRH). Zoladex® 3.6 mg 1-month depot was approved for the treatment of advanced prostate cancer on December 29, 1989. Approval for the treatment of endometriosis was obtained February 2, 1993 and for the treatment of breast cancer December 18, 1995. The current submission to NDA 19-726, dated June 28, 1996 contains clinical information to support the approval of Zoladex® 3.6 mg, 1-month depot for the treatment of endometrial thinning.

It is stated in the current submission that the pharmacokinetic and pharmacodynamic studies in females were submitted in the supplement (Serial No. 005) submitted to NDA 19-726 on July 31,1991 and that no new studies are provided in this application. Table 1 includes the mean pharmacokinetic data from the bioreview by Tien-Mien Chen, Ph.D., Division of Pharmaceutical Evaluation II (HFD-870) dated November 4, 1992, of supplement (Serial No. 005) submitted on July 31, 1991. These studies were deemed adequate to satisfy the clinical pharmacology and biopharmaceutics requirements for approval of Zoladex® 3.5 mg 1-month depot for the indications in females it is currently marketed (endometriosis and breast cancer).

Table 1. Mean (SEM) Pharmacokinetic Data Summary

Design	N	Diagnosis	Dose #	Tmax (d)	Cmax (ng/ml)	AUC (ng*d/ml)	CL (ml/min)
Single Dose	9	healthy volunteers	1	14	1.19 (0.19)	17.8 (1.9)	153.3 (15.5)
Multiple Dose	6	Menorrhagia or uterine fibroids	1	11.5	1.37 (0.37)	17.4 (2.8)	160.2 (22.3)
			2	15	1.45 (0.33)	18.5 (4.2)	163.9 (29.0)
Multiple Dose	14	Polycystic Ovary Syndrome	1	16	1.75 (0.29)	17.5 (2.3)	169.3 (21.6)
			2	16	1.69 (0.17)	19.4 (1.8)	141.9 (12.6)
			6	15	2.36 (0.45)	21.1 (2.8)	136.9 (18.9)
Multiple Dose	8	Endometriosis, menorrhagia, PMS, or uterine fibroids	1	15	1.40 (0.22)	16.2 (1.9)	166.0 (17.0)
Multiple Dose	46	Uterine Fibroids	1	—	1.35 (0.13)	17.36 (1.21)	160.9 (11.9)
			6	—	1.48 (0.21)	19.15 (2.53)	167.8 (14.9)

It is also stated in the submission that the to-be-marketed formulation included herein is identical to that for the currently approved and marketed indications and no changes regarding the chemistry, manufacturing and

controls are being made to the product to support the indication of endometrial thinning.

Comments:

1. The studies previously submitted to the Agency using Zoladex® 3.6 mg depot were not conducted in the target population for the indication sought in this submission (endometrial thinning). However, it is apparent from the data previously submitted (Table 1) that the pharmacokinetics of goserelin acetate do NOT appear to be effected by the diagnoses that have been tested. Additionally, it is not expected that the current indication will have any effect on the pharmacokinetics of Zoladex® 3.6 mg Depot.

2. In a conversation with Dr. Craig Cropp, Medical Officer, Division of Reproductive and Urologic Drug Products (HFD-580), FDA, it was stated that no additional pharmacodynamic analysis (estradiol suppression, etc.) from the clinical studies was necessary in the review of NDA 19-726, supplement S-018 for the indication of endometrial thinning.

3. The proposed label is included in Attachment 1.

4. In the **Clinical Pharmacology** section, **Pharmacokinetics** sub-section of the label, the following change in headings should be made;

Recommendation:

It is the recommendation of the Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPEII) that the sponsor has previously provided sufficient clinical pharmacology and biopharmaceutic information to support the indication of endometrial thinning and supplement (Serial No. 018) to NDA 19-726 for Zoladex® 3.6 mg 1-month depot is acceptable.

The Recommendation and Comment 4 should be communicated to the sponsor as appropriate.

K. Gary Barnette, Ph.D.
Office of Clinical Pharmacology and Biopharmceutics
Division Pharmaceutical Evaluation II

RD initialed by Angelica Dorantes, Ph.D., Team Leader AD 1/10/97
FT signed by Angelica Dorantes, Ph.D., Team Leader Dorantes 1/10/97

cc: NDA 19-726, HFD-580 (Cropp, Dunson), HFD-870 (ML.Chen, Hunt, Dorantes, Barnette), HFD-340 (Viswanathan), Drug file (Millison, HFD-850).

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