CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19726/S18

PHARMACOLOGY REVIEW(S)

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N19726.s018

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NDA 19-726

Zeneca Limited
Macclesfield, England
US Agent: Zeneca Pharmaceuticals
Wilmington, DE

Submission dated: 6-28-1996 Received at HFD-510: 6-28-1996

Pharmacology Review of NDA Supplement S-018

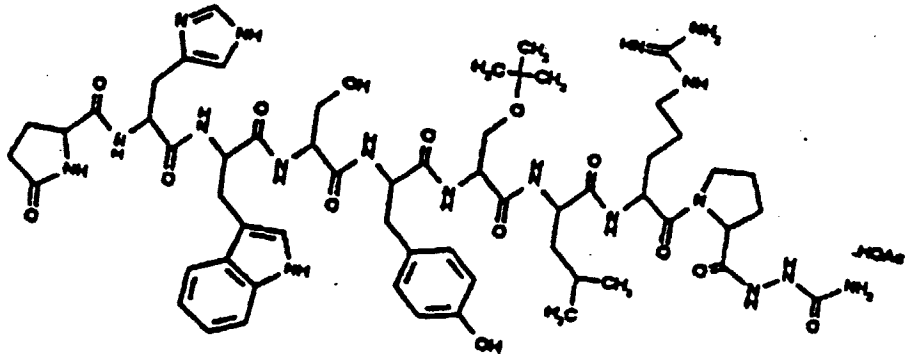
Drug Product:

Established name: Goserelin acetate implant
Proprietary name: Zoladex
Code name: ICI 118,630
Chemical name: 1-(5-oxo-L-propyl-L-histidyl-L-tryptophyl--seryl-L-tyrosyl-O-tert-butyl-D-seryl-L-leucyl-L-arginyl-L-prolyl)semicarbazide; [D-Ser(Bu^t), $Azgly^{10}$]LH-RH.

Molecular formula: $C_{59}H_{84}N_{18}O_{14} \cdot (C_2H_4O_2).x$ x= 1 to 2.4

Molecular weight: 1269

Structural formula of goserelin acetate:



Previously approved indications: Palliative treatment of advanced prostate carcinoma, management of endometriosis and treatment of breast cancer.

Proposed indication: Endometrial thinning prior to endometrial ablation. Dosing recommendation is for 2 depots administered 28 days apart with surgery timed within 2 weeks after the second depot.

Strength: 3.6 mg

Dosage form and route of administration: Implant, subcutaneous

Related INDs and NDAs:

INDs

NDAs	Indications	Date approved
19-726	Prostate cancer	December 29, 1989
19-726,S-005	Endometriosis	February 2, 1993
20-515	Breast cancer	December 18, 1995

Zoladex is a potent synthetic decapeptide agonist analog of the naturally occurring hormone known as luteinizing hormone-releasing hormone (LH-RH) or gonadotropin releasing hormone (GnRH). It differs from naturally occurring hormone in substitutions made at positions 6 and 10 of the peptide as shown in the chemical and structural formulae.

The pharmacologic effects of Zoladex result from its occupation of the LHRH receptors on the pituitary, which disappear from the surface by being internalized. This results in initial stimulation resulting in supra physiologic secretion of FSH and LH. Continued presence of Zoladex results in loss of pituitary LHRH receptors with subsequent inability to respond to continuous Zoladex administration, a phenomenon called as down-regulation.

Reduction of LH secretion by the pituitary gland results in low levels of estrogen production by the ovaries, gonadal atrophy, and reduced tissue mass of estrogen-sensitive reproductive

organs, effects which are reversible on Zoladex discontinuation.

It is based on its above mechanism of action that Zoladex is used in the treatment of advanced prostatic carcinoma, in women with endometriosis and for the treatment of premenopausal and perimenopausal women with advanced breast cancer.

Zoladex's pharmacological effect of diminishing concentrations of circulating estrogen results in atrophy of endometrium and thus has the potential for use as an adjunct treatment for women undergoing hysteroscopic ablation as treatment for conditions such as dysfunctional uterine bleeding proposed under this submission.

Nonclinical Pharmacology and Toxicology: All preclinical pharmacology and toxicology has been referred to previously submitted INDs and approved NDAs for various indications.

Labeling: Current approved labeling for Zoladex 3.6 mg implant has been modified to include proposed changes for endometrial thinning.

Recommendations: Based on extensive preclinical and clinical experience on the safety and efficacy of Zoladex implant along with results of the clinical studies conducted to support its proposed use as endometrial thinning agent prior to endometrial ablation for dysfunctional uterine bleeding, Pharmacology considers it safe and recommends approval of Zoladex implant for the proposed indication.

Krishan L. Raheja 7/23/96
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A Jordan 7/23

Original NDA 19-726 S-018
HFD-345
HFD-580
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