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APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-344

Clinical Pharmacology and Biopharmaceutics Review

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS NDA REVIEW

NDA number, type: NDA 21-344, 1S

Brand name: FASLODEX® Injection

Generic name: fulvestrant

Type of dosage form and strength(s): pre-filled syringes, 2.5 ml (125 mg) and 5 ml (250 mg)

Indication(s): FASLODEX is indicated for the

DRAFT

Applicant name: AstraZeneca Pharmaceuticals, LP

Submission (letter date): initial (March 28, 2001)
BB (November 13, 2001)
C (December 31, 2001)
BB (January 30, 2002)

OCPB and ORM Division names: Division of Pharmaceutical Evaluation 1 and Division of Oncologic Drug Products

OCPB Reviewer(s) and Team Leader names: Gene Williams, Ph.D. and N.A.M. Rahman, Ph.D.

Type of Submission: New Drug Application (NME)

I. Executive Summary

A. Recommendations

The Clinical Pharmacology and Biopharmaceutics portion of this NDA is acceptable. No new risk management recommendations have resulted from this review.

B. Phase 4 commitments

A single Phase 4 commitments is recommended. We recommend that the Applicant perform a study of the effect of ketoconazole on fulvestrant pharmacokinetics. For ease, to allow for fewer patients (the IV route has less inter-individual variability than the IM route) and to increase safety during performance of the study, we recommend that this study be conducted using the intravenous formulation of fulvestrant.

II. Table of Contents

Glossary

^{14}C – radioactive carbon (molecular weight = 14)
AUC – area under the concentration versus time curve
Cl -- clearance
Cmax – maximum concentration
Cmin – minimum concetration: the concentration just prior to the next dose
Ctrough – minimum concetration: the concentration just prior to the next dose
CV – coefficient of variation
CYP – cytrochrome P450
ER – estrogen receptor
FSH – follicle stimulating hormone
Gmean – geometric mean
HDL – high-density lipoprotein
IM – intra-muscular
in vitro – not in humans or animals
in vivo – in humans or animals
IV – intra-venous
kg – kilogram
L – liter
LA – long-acting
LDL – low-density lipoprotein
LH – lutenizing hormone
mg – milligram
min – minute(s)
ml – milliliter
NDA – New Drug Application
NME – new molecular entity (a molecule not previously approved as a human drug)
OCPB – Office of Clinical Pharmacology and Biopharmaceutics
P450 – cytochrome P450
PD – pharmcodynamic(s); a measure of drug effect
PgR – progesterone receptor
Phase 4 – the post-approval stage of drug development
PK – pharmacokinetic(s)
PK/PD – relating concentration (PK) to effect (PD)
POSTHOC – an analysis option within the NONMEM software program
Q – once every
SA – short-acting
Tmax – time at which maximum concentration (Cmax) is reached or was measured
V – volume of distribution
Vd – volume of distribution of the central compartment
VLDL – very-low-density lipoprotein
Vss – steady-state volume of distribution
µM – micromolar or micromoles

III. Summary of Clinical Pharmacology and Biopharmaceutics Findings

In vivo and *in vitro* data support the following conclusions:

- In clinical use, drug exposure is controlled by the properties of the LA IM injection
    - the ratio of Cmax to Ctrough for a 5 ml IM injection and a 28-day inter-dose interval is approximately 2.5.
    - On a Q 28-day regimen, levels approach approximate steady-state after 3 doses.
    - the pharmacokinetics of fulvestrant 250 mg were shown to be similar when administered as either a single 5-ml or as two 2.5-ml injections.
    - no clear relationship has been established between efficacy measurements (time to progression, objective response) and pharmacokinetic parameters such as Cmax, Cmin, AUC, and clearance.
- The general pharmacokinetics are:
    - fulvestrant is rapidly distributed following administration by IV infusion, with plasma concentrations decreasing rapidly in a multiexponential fashion. Estimates of mean terminal elimination half-lives range from approximately 14.0 to 18.5 hours.
    - fulvestrant is rapidly cleared (>10 ml/min/kg) and renal elimination is low (i.e. <1%).
    - fulvestrant is extensively metabolized.
- No meaningful differences in the pharmacokinetics are apparent between male and either pre- or postmenopausal female subjects following administration of a single IV dose, nor between male and postmenopausal female subjects following IM administration (irrespective of age).
- Fulvestrant has been shown to be highly bound (99%) to plasma proteins (predominantly lipoproteins) and to have a large steady-state volume of distribution (approximately 3 to 5 L/kg), which suggests that the distribution of the compound is largely extravascular.
- Preclinical studies with human cytochrome P450 isoenzymes and results from clinical pharmacokinetic trials involving the co-administration of fulvestrant with midazolam or rifampin suggest that

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