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APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-344

Pharmacology Review(s)

Pharmacology/Toxicology Review of NDA 21-344

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Subject: NDA 21-344
FASLODEX®® Injection (fulvestrant)
Secondary Review of Pharm./Tox. Information and Product Label

I. Materials Included in Review

1. Pharm./Tox. Review of NDA 21-344, written by Lilliam A. Rosario, Ph.D.

II. Background

The sponsor (AstraZeneca Pharmaceuticals, LP.) is seeking approval of FASLODEX® (injection) for use in Draft

FASLODEX® (fulvestrant) is a modified steroid, which binds competitively to the estrogen receptor (ER), with an affinity approximately comparable to that of estradiol. Fulvestrant acts as a competitive inhibitor of the activation of the ER by estradiol, and thereby inhibits the growth of ER+ dependent tissues.

III. Comments and Conclusions

1. A review of NDA 21-344, FASLODEX® Injection (fulvestrant), indicates the product has been adequately evaluated in multiple repeat-dose non-clinical safety studies (including: acute and repeat-dose (IM) toxicology studies up to 6 and 12 months in rats and dogs), reproductive toxicity tests in rats and rabbits (Segments I-III; ICH endpoints A-F), genotoxicity tests (in vitro and in vivo), and in two carcinogenicity bioassays (in mice and rats), for approval in the treatment of postmenopausal women with locally advanced or metastatic breast cancer who have previously been treated with endocrine therapy. It should be noted that the carcinogenicity testing and full spectrum of reproductive toxicity studies performed by the sponsor were not deemed necessary by the Review Division for potential product use in a postmenopausal patient population with advanced neoplastic disease.

2. Specific comments pertaining to the product review follow.

Genotoxic and Carcinogenic Potential:

In a 2-year carcinogenesis study in rats (male and female), an increased incidence of benign ovarian granulosa cell tumors and testicular Leydig cell tumors was evident, in females dosed at 10 mg/rat/15 days and males dosed at 15 mg/rat/30 days, respectively. Induction of such tumors is consistent with the pharmacology-related endocrine feedback alterations in gonadotropin levels caused by an anti-estrogen. Fulvestrant showed no antigenic, mutagenic, or clastogenic potential in a standard battery of genotoxicity tests when evaluated at doses or concentrations appropriate to the assay.

Following review of the carcinogenicity data by the Executive Committee of the CAC (Carcinogenicity Assessment Committee), it was recommended by the executive committee that the sponsor be asked to conduct a P32 post-labeling assay for the formation of DNA adducts by fulvestrant (or its' metabolites). This request was apparently based on previous experience with tamoxifen (a related competitive inhibitor of the ER), which when tested for carcinogenic potential yielded positive results in multiple hormonally dependent tissues and caused an increased incidence of hepatic tumors (which could not be explained as dependent upon ER activity). When subsequently tested in the P32 post-labeling assay, it was found that exposure to tamoxifen resulted in the formation of DNA adducts (a likely explanation for the increased incidence of hepatic tumors).

As stated above, dosing with fulvestrant for up to 2 years resulted in an increased incidence of benign ovarian granulosa cell tumors and testicular Leydig cell tumors, in females dosed at 10 mg/rat/15 days and males dosed at 15 mg/rat/30 days, respectively. There was no evidence in the study of fulvestrant for the increased induction of tumors in any non-hormone dependent/sensitive tissue. Furthermore, fulvestrant showed no mutagenic or clastogenic potential in a standard battery of genotoxicity tests. Based on this data, it does not appear that further testing of the genotoxic potential of fulvestrant is necessary for product approval.

Mechanism of Action:

Fulvestrant binds ER in a competitive manner, with a high affinity comparable to that of estradiol. The Sponsor claims that "Fulvestrant is a potent antiestrogenic agent, which acts by down-regulation of the estrogen receptor (ER) inducing a rapid loss of ER protein from breast cancer cells. Preclinical studies demonstrated that fulvestrant is a potent, reversible inhibitor of the growth of estrogen- sensitive human breast cancer cells and of tamoxifen- resistant breast cancer cells in vitro. The sponsor appears to be intending to use this data as support for defining fulvestrant as a new class of antiestrogen, one that acts via a new mechanism. However, several issues, which should be considered as part of this topic, are outlined in the following paragraphs.

A) In a study by Robertson et. al. (2001), it was found that immuno-reactive ER was reduced in tissues taken from postmenopausal women with breast cancer, who were treated with either fulvestrant or tamoxifen prior to surgery. While the dosing interval was limited in duration, this data does not appear to support the sponsor's contention that fulvestrant functions via a new and unique mode of action (dissimilar to the mode of action of tamoxifen).

B) Throughout the MOA studies conducted by the sponsor, ER protein levels were measured by an indirect immuno-reactive assay methodology, as compared to direct receptor isolation/purification and protein analysis. Furthermore, the sponsor did not provide affinity data for the specificity of the ER antibodies, or data for effects of conformational changes that might occur with bound fulvestrant, tamoxifen or estradiol, and how this might alter antibody binding to the ER. It is therefor recommended that the product label clearly specify that ER protein was measured via an immuno-reactive assay (vs. direct protein measurement).

Taken together, these data do not appear to support the sponsors' contention that fulvestrant functions through a unique mode of action (i.e., ER protein down-regulation), which is independent of the mode of action of tamoxifen.

3. Specific comments pertaining to the product label follow.

A review of the draft product label suggests that it adequately reflects the non-clinical safety profile of fulvestrant injection.

IV. Summary

A review of the action package for NDA 21-344, FULVESTRANT® Injection, suggests that the product has been adequately evaluated in multiple non-clinical safety studies for potential approval in the [redacted] There are no unresolved issues or requests to be directed to the sponsor for this indication.

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